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Discovery

Application of Hydrotalcite as green catalyst for synthesis of intermediates of antihypertensive agents

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ABSTRACT

N-alkylation of Imidazole derivative with substituted bromo methyl biaryl is an important reaction in organic chemistry especially in the synthesis of various intermediates of sartans. The reactions thus far have been limited to the usage of different organic and inorganic bases. The present investigation explores a novel, eco-friendly, industrially scalable and efficient approach for the synthesis of intermediates of different antihypertensive agents or sartans including usage of catalytic amount of Hydtotalcite as base instead of conventional bases. This methodology overcomes many of drawbacks associated with conventionally reported synthesis.

Keywords: Antihypertensive intermediates, N-alkylation, Hydrotalcite clay, E-factor.

Abbreviations: E-Factor - Environmental Factor

1. INTRODUCTION

Hypertension (high blood pressure) is a common disease observed in the present age due to abnormal lifestyle of human. It is auspiciously treated by a class of drugs known as antihypertensive. Such kind of therapy looks for the prevention of complications such as stroke and myocardial infarction. There are many classes of antihypertensive, which lower blood pressure by different means.[1] Valsartan, Telmisartan, Losartan, Irbesartan, Azilsartan, Candisartan, Olmesartan Medoxomil, etc. are considered under one of the class of antihypertensive agents.

Application of Hydrotalcite as cationic clay during the chemical transformation included in synthesis of antihypertensive agents is considered as green chemical approach because clay is a widely distributed, abundant mineral resource of major industrial importance for an enormous variety of uses.[2] It also provides specific features like high versatility, wide range of preparation variables, use in catalytic amounts, ease of set-up and work up, mild experimental conditions, easy work – up procedure, gain in yield and/or selectivity, low cost, recyclability etc. These properties make them more applicable towards establishing environmentally benign technologies.[3]

The cationic clays are solid base catalysts which provide the opportunity for environmentally friendly ("green") synthesis of fine chemicals and pharmaceuticals that conventionally involve large amount of harmful and unrecoverable reagents such as inorganic or organic bases i.e. NaOH, KOH, Triethylamine, Pyridine etc.[4, 5] Typical solid base catalysts, such as Hydrotalcites are double-metal hydroxides consisting of both anionic and cationic characters which are useful in acting a vital role in different organic transforms e.g. monooxygenations and carbon – carbon bond formations including aldol condensation, Knovengel reaction, and Michael addition.[6] The interesting field of application of

Hydrotalcite is that it can be used as an effective substituent for the inorganic as well as organic bases which are being used in the pharmaceutical industries in bulk quantity for the synthesis of different categories of Active Pharmaceutical Ingredients. Also as the Hydrotalcite is heterogeneous catalyst, it can be reused and recycled so as to reduce the value of E factor and atom efficiency.[7, 8]

The first general metric for green chemistry is Roger Sheldon's E-factor can be defined by the ratio of the mass of waste per unit of product.

E-factor = Total waste (kg) / Product (kg)

The ideal value of E factor = 0 which is almost achieved in petroleum refining which is the sign of best environmental impact while for higher value of E factor means greater negative environmental impact as more waste generating.[9] In case of fine chemical and pharmaceuticals industries, E-factor is in 5 – 50 and 25 – 100 respectively i.e. more waste is generated in these industries.

Hydrotalcite, first discovered in Sweden around 1842[10] is a layered double hydroxide (LDH) whose name is derived from its existence with talc and high water content.

$$Mg_6 Al_2 (OH)_{16} CO_3 . 4H_2O$$

The weakly bounded carbonate anions laid between the structural layers improve the anion exchange capabilities of hydrotalcite.[11] Hydrotalcite comprises layered materials with positively charged layers and weakly bounded anions. These anions behave charge-balancing anions, often exchangeable, located in the interlayer region.[12] LDHs are derived from the structure of mineral brucite, $Mg(OH)_2$. Each bracket consists of a hexagonal close-packing of hydroxyl ions in which alternate layers of octahedral sites are occupied by Mg^{+2} ions. This results in the stacking of charge-neutral hydroxide layers of the composition $Mg(OH)_2$[13, 14]

When a fraction, x, of the Mg^{+2} ions in brucite is substituted by trivalent cations such as Al^{+3}, the resultant hydroxide layers having the composition $[Mg_{1-x}Al_x(OH)_2]^{x+}$ acquire a positive charge and intercalate various anions, An- , in the interlayer region. These results in the expansion of the c-parameter (Figure 1) from 4.8 Å, which is seen in brucite, to 7.7 Å observed in hydrotalcite. (x = 0.25, $An^- = CO_3^{2-}$) [10, 15] Material of this type exhibit anionic (hydroxyl ion) mobility, anion exchange and sorption properties in addition to surface basicity, making them attractive catalysts for the base catalyzed reactions.[16]

Hydrotalcite could be a powerful etiquette for the stipulation of immobilized hydroxyl groups on its surface and these possibly may be used as heterogeneous base catalysts for chemical reactions. Calcined hydrotalcites contain surface Bronsted weakly basic OH^- groups, Lewis medium (Mg–O pairs) and strong basic sites related to isolated O^{-2} anions.[17] Also inter layered CO_3^{2-} species may further empower the basicity of it.[5]

Our efforts are focused on the introduction of novel green chemical pathway over the existing hazardous waste generating pathway utilizing the catalytic amount of Hydrotalcite as solid base within the molecular frame work in order to synthesizing pharmacologically interesting antihypertensive intermediates. These are designed, generated and characterized using spectral studies.

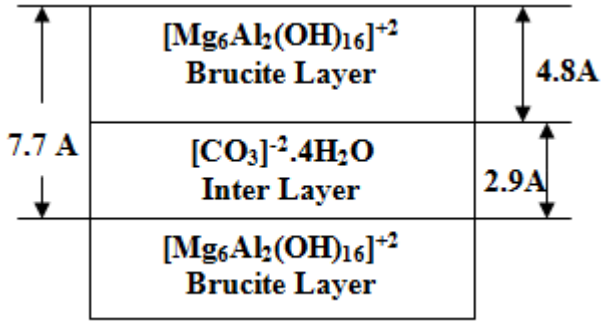
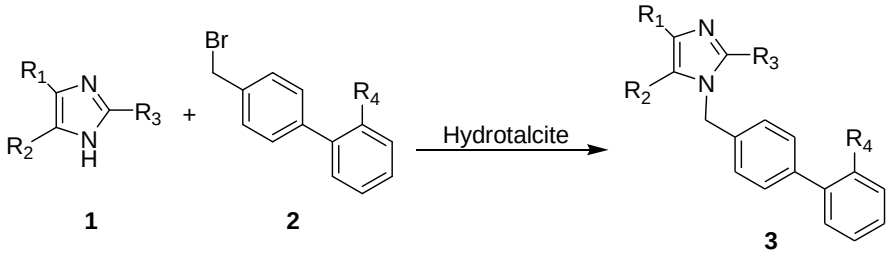


Figure 1
Unit Cell of Hydrotalcite

Another objective of the present manifestation is to prove the process efficiency and industrial applicability by making comparison of E-factors of both the conventional as well as present work.

The synthesis of intermediates of different antihypertensive agents is described in below mentioned (scheme 1). Here the N-alkylation of imidazole derivative **(1)** with substituted bromo methyl biaryl compound **(2)** by catalytic amount of Hydrotalcite as base provides the key organic intermediate **(3)** of some sartans.



Scheme 1
N-alkylation of Imidazole derivative with substituted bromo methyl biaryl compounds

2. MATERIALS AND METHODS

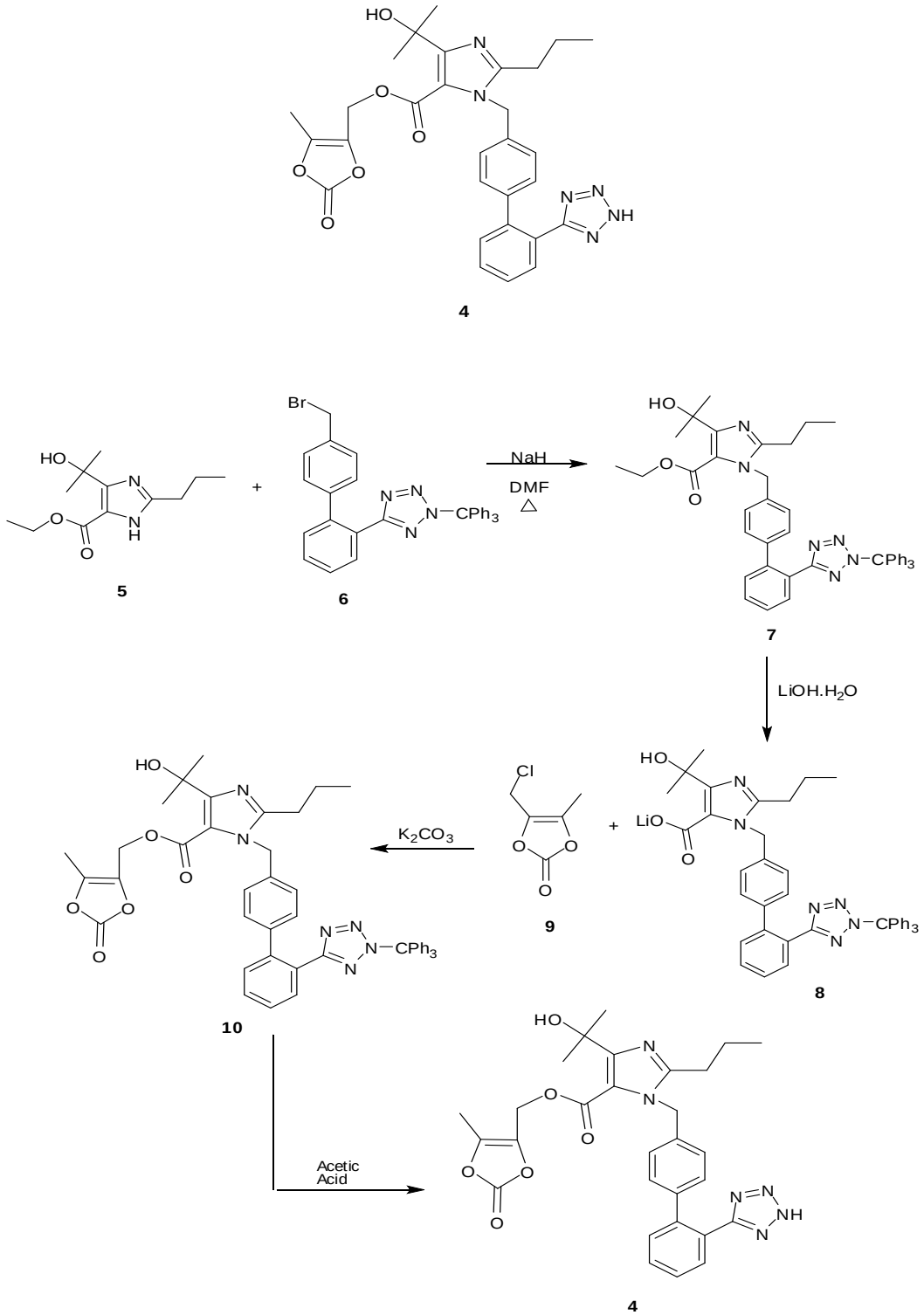
All the Key Staring Materials were used from commercial production batches at Amoli Organics Pvt. Ltd. Vadodara. The Hydrotalcite was purchased from Sigma – Aldrich.

The ^1H NMR spectra were measured in DMSO-d6 using 400MHz operating frequency on a BRUKER AV – 400 FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as a KBr dispersion using Shimadzu FTIR Prestige 21 Spectrophotometer over the range of 4000 – 400cm^{-1} with a resolution of 5 cm^{-1}. The mass spectrum was recorded on HP-5989 LC-MS spectrometer. While the chromatographic purity of all the intermediates were confirmed on High Performance Liquid Chromatography Shimadzu. All the melting points are taken in an open capillary and uncorrected. In addition to these, the reaction progress was monitored by Thin Layer Chromatography system.

2.1. Synthesis of Olmesartan Medoxomil Intermediates

Olmesartan Medoxomil **(4)** is an antihypertensive agent. It belongs to the category of medications called angiotensin II receptor

blockers. It is approved for the treatment of high blood pressure and is marketed under the trade name Olmetec.[18] The prior art synthetic method for Olmesartan Medoxomil is given as per following (scheme 2).[19]



Scheme 2

Prior art synthetic route of Olmesartan Medoxomil

Olmesartan Medoxomil is prepared from condensation of 1H-Imidazole-4-carboxylic acid, 5-(1-hydroxy-1-methylethyl)-2-propyl-, ethyl ester **(5)** with N-(triphenylmethyl)-5-[4'-(Bromomethyl biphenyl)-2-yl]tetrazole **(6)** using sodium hydride as base in DMF as solvent at 60°C to give ethyl 5-(2-hydroxypropan-2-yl)-2-propyl-1-((2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-

imidazole-4-carboxylate **(7)** as intermediate. The intermediate thus obtained is hydrolyzed by lithium hydroxide monohydrate as base in 1,4-dioxane at 5-10°C to give lithium salt **(8)** of the above intermediate which is coupled with 5-methyl-2-oxo-(1,3-dioxolene-4-yl)methyl chloride **(9)** using potassium carbonate as base in DMF as solvent at 50°C to give trityl protected olmesartan medoxomil **(10).** This tritylated Olmesartan medoxomil is de protected by aqueous acetic acid solution giving Olmesartan Medoxomil **(4)** as final API.

Various impurities are formed and isolation of the product involves extractive workup and column chromatography. It is a long-felt need to provide improved process that can be performed on a commercial scale, without the need for chromatographic purification, does not use carcinogenic solvents and multi step extractive work up to give olmesrtan medoxomil in high purity.[20]

Ethyl 5-(2-hydroxypropan-2-yl)-2-propyl-1-((2'-(1-trityl-1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-1H-imidazole-4-carboxylate 7 or (Olmesartan Intermediate 1)

1H-Imidazole-4-carboxylic acid, 5-(1-hydroxy-1-methylethyl)-2-propyl-, ethyl ester **5** 10.0 g (0.416 mole) was treated with 6.3 g Hydrotalcite (0.01 mole) at 25 – 30°C for 15 min in 50 ml N,N-dimethyl acetamide as solvent giving white suspension. To this suspension, charged 24.58 g (0.044 mole) N-(triphenylmethyl)-5-[4'-(Bromomethyl biphenyl)-2-yl] tetrazole **6** at same temperature and stirred for 15 min. 1.192 g (3.69 mmole) tetra butyl ammonium bromide was charged at same temperature to give suspension. The whole reaction mass was heated up to 40 – 45°C and allowed to stir for further 8 – 10 h to give ethyl 5-(2-hydroxypropan-2-yl)-2-propyl-1-((2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-4-carboxylate **7** as intermediate . The progress of reaction was monitored on Thin Layer Chromatography. After completion of reaction, cool the reaction mass upto 25 – 30°C. The suspended Hydrotalcite was filtered and dried till constant weight is obtained and again reused as catalyst according to description as above. While the clear filtrate was cooled to 15 – 20°C. To this filtrate, 20 ml process water was added to give precipitation of crude intermediate **7** which was filtered and washed with 10 ml water. Further it was recrystalized from 90 ml Acetone to afford pure Ethyl 5-(2-hydroxypropan-2-yl)-2-propyl-1-((2'-(1-trityl-1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-1H-imidazole-4-carboxylate or Olmesartan Intermediate 1, (24.8 g, 83.2 %) having melting point 168 – 170°C (from Acetone).

Purity by HPLC: 99.73 %

IR absorptions: ν_{max}/cm^{-1} 1663_S (CO), 1522m (C-C aromatic), 1290_s (CN aromatic amine), 1447_m (CH alkanes), 1175_m (CN aliphatic amine), 881_S (CH aromatic), 695_m (C=C), 635_m (C-Br)

^{1}H-NMR:

δ_H(400 MHz; DMSO)

δ: 7.8 - 7.7(1H, m, Ar-H), 6.8-7.6 (22H, m, Ar-H), 5.44 (1H, s, -OH), 5.40(2H, s, $-CH_2$), 4.04 - 4.09 (2H, q, $-CH_2$), 2.50 (2H, t, $-CH_2$), 1.48 (6H, s, $-C(CH_3)_2$), 1.48 - 1.57(2H, m, $-CH_2$), 0.97- 1.00(3H, t, $-CH_3$), 0.76 - 0.8(3H, t, $-CH_3$).

Mass: *m/z* 718 (M^+, 25%), 716 (45), 642 (15), 658 (8), 243 (20), 253 (15), 329 (10), 405 (9), 363 (2)

Calculation of E-Factor: Refer Table 2 & Table 3

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl4-(2-hydroxypropan-2-yl)-2-propyl-1-((2'-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate 10 or (Olmesartan Intermediate 2)

In 250 ml round bottom flask, charged 80 ml Isopropyl alcohol and 2.28 g Potassium hydroxide (0.0407 mole) and allowed to stir it for 2 h to get clear solution at 25 – 30°C. To this solution, charged 20 g (0.028 mole) ethyl 5-(2-hydroxypropan-2-yl)-2-propyl-1-((2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-4-carboxylate **7** as obtained in above example at 25 – 30°C. The whole reaction mass was heated up to 40 – 45°C till the completion of reaction. The progress of reaction was monitored by Thin layer Chromatography. After completion of reaction, distilled out whole solvent from reaction mass to get residue which was stripped out by 20.0 ml of Ethyl acetate under reduced pressure to get again solid residue. The residue was dissolved in 40 ml N,N-dimethyl acetamide as solvent and charged 1.05 g (0.0017 mole) Hydrotalcite as base followed by 1.0 g (0.0031 mole) tetra butyl ammonium bromide as phase transfer catalyst at 25 - 30°C. The suspension was cooled up to 10 – 15°C and to it, charged 6.3 g (0.0424 mole) 5-methyl-2-oxo-(1,3-dioxolene-4-yl)methyl chloride **9** between 10 – 15°C. The reaction mass was cooked at 45 – 50°C for 8 – 12 h. The progress of reaction was monitored by Thin Layered chromatography. After completion of reaction, the mass was cooled to 10 – 15°C and filtered to get suspended hydrotalcite. The filtered hydrotalcite was dried till constant weight is obtained and again reused

as catalyst same as described as above. To the clear filtrate, added mixture of 60.0 ml water – 100.0 ml MDC between 10 – 15°C. The organic layer was separated from the solution and washed with 40.0 ml water followed by drying over sodium sulfate. The solvent was removed under reduced pressure to get thick oily residue. The thick oily residue was treated with 100 ml methanol at 25 – 30°C for 2 h to offer thick slurry which was filtered to offer pure intermediate as (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2'-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate or Olmesartan Intermediate 2 (19.6 g, 87.7%) having melting point 107 - 111°C (from Methanol)

Purity by HPLC: 97.48 %.

IR absorptions: ν_{max}/cm^{-1} 3383b (-OH alcohol), 1803s (Cyclic carbonate), 1742s (-COO ester), 1493m (C- C in ring), 1395s (C-H alkane), 1358m (C-H alkane) , 1310s (C-O alcohol), 1144m (C-N), 1003s (=C-H alkene), 957m (-OH alcohol), 925m (C-H aromatic),

^{1}H-NMR:

δ_H(400 MHz; DMSO)

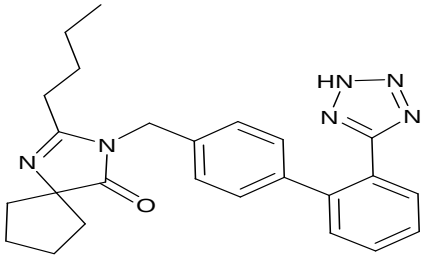
δ: 7.8 (1H, d, Ar-H), 6.88 - 7.7 (20H, m, Ar-H), 6.78 (2H, d, Ar-H), 5.41 (1H, s, -OH), 5.28 (2H, s, $-CH_2$), 5.0 (2H, s, $-CH_2$), 2.44 (2H, t, $-CH_2$), 2.0 (3H, s, $-CH_3$), 1.5-1.56 (2H, m, $-CH_2$), 1.49 (6H, s, $-C(CH_3)_2$), 0.72 - 0.76 (3H, t, $-CH_3$).

Mass: *m/z* 800 (M^+ 55%), 253 (10), 243 (52), 210 (55), 165 (100), 152 (2), 113 (30), 77 (33), 69 (23)

Calculation of E Factor: Refer Table 4 & Table 5.

2.2. Synthesis of Irbesartan Intermediate

Irbesartan **11** is an angiotensin II receptor antagonist used for the treatment of hypertension. It is useful as angiotensin antagonists, particularly angiotensin-II antagonists. It inhibits the action of angiotensin II on its receptors and thus prevents the increase in blood pressure produced by the hormone receptor interaction. Thus, Irbesartan is useful for the treatment of hypertension and heart failure.[21]



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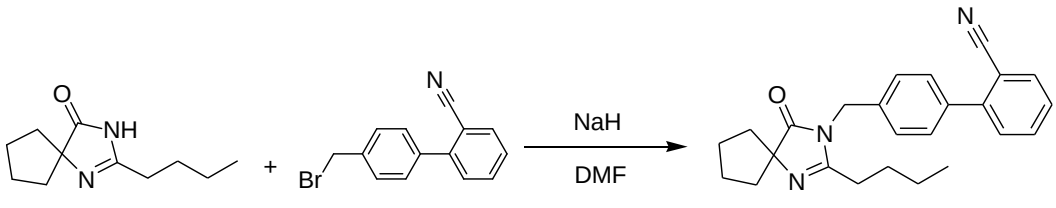
The synthesis of Irbesartan is first disclosed in US patent no 5270317 (equivalent EP 0454511) and subsequently, several other patents disclose the synthesis of it by different methods.[22-26]The prior art synthetic method for intermediate of Irbesartan is given in (scheme 3).



12 **13** **14**

Scheme 3

Prior art Synthetic route of Irbesartan intermediate

A comprehensive review of the above innovative work reveals use of column chromatographic purification of intermediate, long reaction times, additional steps of protection and deprotection, processes resulting in low yields, multistep extractive workup procedures. There is a long felt need of the industry to provide a commercially scalable process of preparing irbesartan which is high yielding as well as eco friendly and devoid of disadvantages described above. The present research relates the same requirements.

2-butyl-3-({4-[2cyanophenyl]phenyl}methyl)-1, 3-diazaspiro [4.4] non-1-en-4-one 14

In a 250 ml three necked RBF, charged 5.0 g (0.026 moles) of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one **12** and 50 ml Acetonitrile at ambient temperature. To this reaction mass, charged 2.5 g (0.0041 moles) Hydrotalcite as base and digest it for 30 min at same temperature. Again charged 5.66 g (0.021 moles) 4-bromomethyl-2'-cyanobiphenyl **13** at ambient temperature. The reaction mass was heated up to refluxing temperature for the next 4 h. Again charged 2.5 g of Hydrotalcite for 3 times at the 4 h of time interval under refluxing condition. Checked the TLC of reaction mass after 16 h of refluxing. On completion of reaction, the whole Acetonitrile solvent was distilled off under vacuum below 45°C to get solid residue. The solid residue was treated with 50 ml Methylene chloride at room temperature to get slurry. The slurry was filtered off to get wet Hydrotalcite form reaction mass which was dried till constant weight is obtained. The above recovered hydrotalcite was reused as catalyst as same as described above. The filtrate was given 50 ml water washing and treated with 1.0 g sodium sulfate to get it dry. Finally it was concentrated under vacuum to give oily residue. The oily residue was treated with mixture of 25 ml Cyclohexane and 5 ml Acetone to give free white crystals as precipitate which were filtered and dried in hot air oven at 50°C to give 2-butyl-3-({4-[2cyanophenyl]phenyl}methyl)-1, 3-diazaspiro [4.4] non-1-en-4-one as intermediate of Irbesartan (8.73 g, 88 %) having melting point 90 – 92°C (from Cyclohexane & Acetone mixture)

Purity by HPLC: 99.42 %.

IR absorptions: ν_{max}/cm^{-1} 3055s (-CH aromatic), 2220s (-C≡N), 1717s (-C=O), 1628s (-C=N-), 1450m (-CH alkane), 1447m (-C-C, in aromatic ring), 1331s (-C-N aromatic amine), 1005s (-C-O).

^{1}H-NMR:

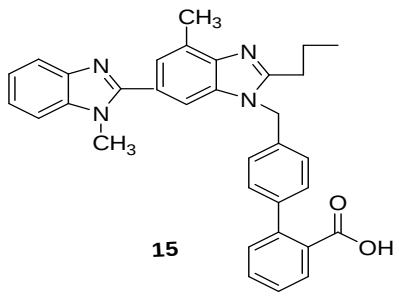
δ_H(400 MHz; DMSO)

δ: 7.8 – 7.33 (8H, m, Ar-H), 4.79 (2H, s, -CH_2), 2.35 - 2.39 (2H, t, -CH_2), 1.86 – 1.69 (8H, m, -CH2 of Cyclo ring), 1.46 – 1.53 (2H, qt, -CH_2), 1.24 - 1.31 (2H, sx, -CH_2), 0.78 - 0.81 (3H, t, -CH_3).

Mass: *m/z* 385 (M^+ 52%), 343 (65), 328 (10), 232 (45), 193 (15), 192 (80), 177 (8), 165 (25).

2.3. Synthesis of Telmisartan Intermediate

Telmisartan **15** is also an angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. In addition to blocking the RAs, Telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism.[27] It is believed that Telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease.[28, 29]



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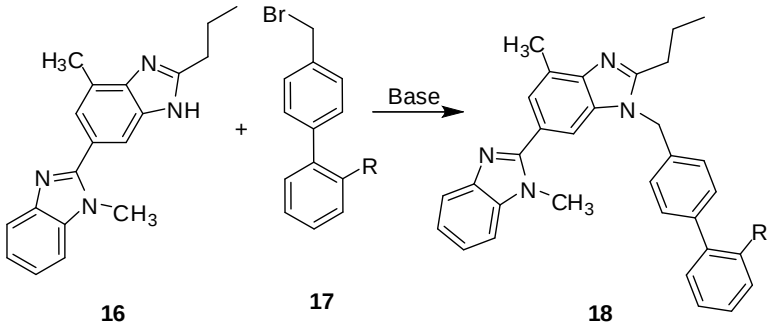
The various synthetic routes for the manufacturing of Telmisartan have already reported in several literatures.[30 – 36] The general reaction as per below scheme 4 consists of condensation of 2-n-propyl-4-methyl-6-(1′-methylbenzimidazol-2′-yl) benzimidazole **16** with 4'-(bromomethyl)biphenyl-2-carbonitrile or alkyl ester of 4'-bromomethyl biphenyl **17** in presence of organic solvents and base

to form 4'-((1,4'-dimethyl-2'-propyl(2,6'-bi-1h-benzimidazole)-1'-yl)methyl)- 1,1'-biphenyl-2-carbonitrile or alkyl ester **(18)** as Key intermediate of Telmisartan of our interest and further hydrolyzed with strong base at 25 - 200°C by using various solvents to produce the Telmisartan hydrochloride or Telmisartan as API.



16 **17** **18**

R = Nitrile or Methyl ester or tert butyl ester

Scheme 4

Conventional Synthetic route of Telmisartan intermediate

The novel synthesis for Telmisartan intermediate which mainly focused on the improved yield and high level of purity with ease of operations without further purification process and low level of effluent and thus meeting all the regulatory norms is described.

4'-((1,4'-dimethyl-2'-propyl(2,6'-bi-1h-benzimidazole)-1'-yl)methyl)-1,1'-biphenyl-2-carbonitrile 18

In a 250 ml three necked RBF, charged 4.5 g (0.0147 moles) of 2-n-propyl-4-methyl-6-(1′-methylbenzimidazol-2′-yl) benzimidazole **16** and 40 ml Acetone at ambient temperature. Allowed to stir the mass for 10 min at 25 – 30°C. To this reaction mass, charged 4.95 g (0.0162 moles) methyl 4'-(bromomethyl)biphenyl-2-carboxylate **17** and 0.51 g (0.00084 mole) hydrotalcite as base. Digest it for 8 h at same temperature. The progress of reaction was monitored by TLC. On completion of reaction, the whole reaction mass was filtered off under vacuum at 25 - 30°C to get wet solid hydrotalcite. The above wet hydrotalcite was dried till constant weight is obtained and it was reused as catalyst in same manner as described above. The filtrate contains intermediate of Telmisartan **18** is concentrated under vacuum at 40 – 45°C to give solid residue which is further recrystallized from 34 ml Acetonitrile to give free crystals as precipitate which are filtered and dried in hot air oven at 60°C to have 4'-((1,4'-dimethyl-2'-propyl(2,6'-bi-1h-benzimidazole)-1'-yl)methyl)-1,1'-biphenyl-2-carbonitrile (6.72 g, 86 %) having melting point 184 – 185°C (from Acetonitrile).

Purity by HPLC: 99.46%.

IR absorptions: ν_{max}/cm^{-1}: 2955m (-CH alkane), 1703s (-C=O), 1614m (-C-C aromatic), 1447m (-C-H alkane), 1383m (-CH alkane), 1287s (-C-O ester), 1267s (-C-N aromatic amine), 1244m (-C-N aliphatic amine), 723m (-C-H alkane)

^{1}H-NMR:

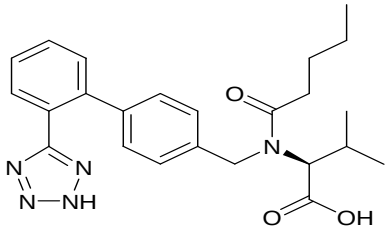
δ_H(400 MHz; DMSO)

δ : 7.20 – 7.77 (14H, m, Ar-H), 5.65 (2H, s, -CH_2), 3.85 (3H, s, -CH_3), 3.5 (3H, s, -CH_3), 2.91 – 2.94 (2H, t, -CH_2), 2.64 (3H, s, -CH_3), 1.78 – 1.83 (2H, m, -CH_2), 1.00 (3H, t, -CH_3)

Mass: *m/z* 528 (M^+ 75%), 225 (95), 44 (100), 77 (10), 303 (28), 275 (20), 152 (17), 500 (4), 513 (1), 165 (82)

2.4. Synthesis of Valsartan Intermediate

Valsartan **19** is non-peptide and a specific angiotensin II receptor antagonist (more commonly called an ARB, or angiotensin receptor blocker), with particularly high affinity for the type I (AT_1) angiotensin receptor.[37, 38] By blocking the action of angiotensin, valsartan dilates blood vessels and reduces blood pressure.



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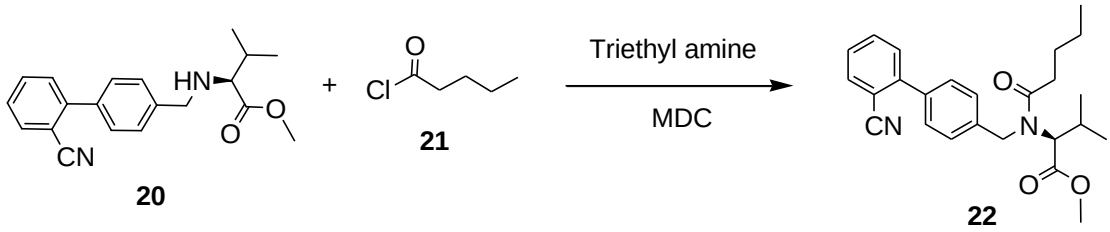
The conservative synthetic route for the preparation of key intermediate of Valsartan **22** is described in the below mentioned (scheme 5).[39]



Scheme 5

Conservative synthetic route for Valsartan key intermediate

Briefly, the process for the preparation of valsartan comprises of the condensation of (S)-methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-methylbutanoate **20** with valeryl chloride **21** in the presence of triethylamine and dichloromethane to give the compound (S)-methyl 2-(N-((2'-cyanobiphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate. **22** Also some other literatures disclose the processes for the synthesis of the same intermediate.[40, 41]The aforementioned process uses triethylamine in the process for the preparation of the compound **22** in which process the reaction is incomplete due to presence of moisture, affecting the quality of the product, leading to a lower yield and requiring flash chromatography for purification. Consequently, there is a long-felt need for a process for the preparation of **22** which not only overcomes the problems in the art processes as mentioned above, but is also safe, cost effective, industrially feasible, clean and eco-friendly.

(S)-methyl 2-(N-((2'-cyanobiphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate 22

In a 250 ml four necked round bottom flask, charged 60 ml Toluene and 30 ml water followed by 10.0 g (0.031 moles) (S)-methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-methylbutanoate **20** at 25 – 30°C. To the reaction mass, charged 0.5 g (0.0016 moles) tetra butyl ammonium bromide, 5.61 g valeryl chloride **21** and 2.8 g (0.0046 moles) hydrotalcite at same temperature. The reaction mass was allowed to stir for 3-4 h at 25 – 30°C. The progress of reaction was monitored on TLC. After completion of reaction, filter the mass to remove wet hydrotalcite. The wet hydrotalcite was dried till constant weight is obtained. The recovered hydrotalcite was reused as catalyst in same manner as described above. The obtained filtrate was separated from aqueous layer to give product in organic layer which was distilled out under vacuum at 60°C to give residue. The residue was dissolved in 30 ml Ethyl acetate and allowed to stir it for 15 min to give clear solution which was washed with 50 ml 2% sodium bicarbonate solution at 25 – 30°C. The organic layer was distilled out under vacuum at 50°C to give (S)-methyl 2-(N-((2'-cyanobiphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate (11.47 g, 91%) as yellow oil.

Purity by HPLC: 98.63 %

IR absorptions: ν_{max}/cm^{-1} 2950m (-C-H Alkane), 2874m (-C-H, Alkane), 2224s (-C≡N, Nitriles), 1735s (-C=O, esters), 1651s (-C=O ketone), 1454m (-C-H Alkane), 1263m (-C-N Aliphatic amine), 762s (-C-H Aromatic).

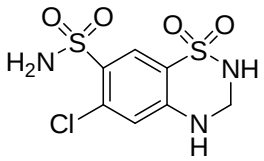
δ_H(400 MHz; DMSO) :

δ : 0.92 – 0.97 (9H, q, -$(CH_3)_2$ & -CH_3), 1.31 – 1.36 (2H, m, -CH_2), 1.67 – 1.75 (2H, m,-CH_2), 2.34 – 2.38 (2H, m, -CH_2), 1.71 – 2.74 (1H, m, -$CH(CH_3)_2$), 3.64 (2H, s, -CH_2), 4.46 – 4.59 (3H, m, -CH_3), 4.90 – 4.94 (1H, d, -CH), 7.42 – 7.81 1.72 (8H, m, Ar-H)

Mass: *m/z* 406 (M^+ 45%), 273 (5), 227 (1), 192 (100), 190 (15), 177 (5), 165 (17), 113 (3), 86 (4)

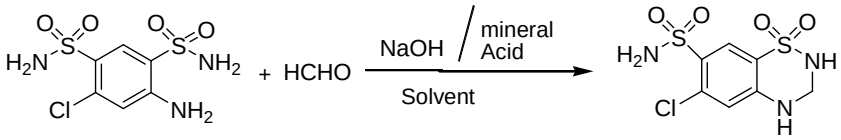
2.5. Synthesis of Hydrochlorothiazide

Apart from Synthesis of intermediates of sartans, we have also develop a robust and economic route for the synthesis of Hydrochlorothiazide **23** as API using the hydrotalcite as base is described below in greater detail. Hydrochlorothiazide is a diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retaain water. It is generally used in combination with antihypertensive drugs such as Irbesartan, Valsartan, Candesartan Cilexetil, Olmesartan, Telmisartan etc.



23

According to conventional method, it is being synthesized by reacting 5-chloro-2, 4-disulfamyl-aniline **24** with Formaldehyde in the presence of a base or mineral acids and a solvent[42] to give 6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide or Hydrochlorothiazide **23**. However, the yield obtained by this process is only 46.3% which makes the process less attractive at an industrial scale. Moreover repeating this experiment, it is found that it results in the formation of dimer impurity along with Hydrochlorothiazide which is difficult to remove by conventional purification methods.



24 **23**

Scheme 6

Reported Synthetic route of Hydrochlorothiazide

6-Chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 23

5-chloro-2, 4-disulfamyl aniline **24** (0.035 mole, 10.0 g) and Para formaldehyde (0.036 mole, 1.071 g) were taken along with 100 ml water in a 250 ml three necked round bottom flask equipped with condenser and a thermometer pocket. The slurry was allowed to stir for 15 min at ambient temperature followed by addition of 200 mg hydrotalcite (0.33 mmole) in the reaction mass. The slurry was heated up to refluxing of solvent for the 6 to 8 h. After completion of reaction, monitored by TLC, the mass was cooled up to ambient temperature to give white crystalline crude Hydrochlorothiazide **23** which was dissolved in 30 ml 25 % aq. Ammonia solution and 20 ml water mixture to give turbid mass. Hydrotalcite was recovered by filtration to give clear filtrate which was decolorized by 0.2 g charcoal. The filtered hydrotalcite was dried till constant weight is obtained and reused in same manner as described above. The clear solution thus obtained was further treated with 12.5 ml 1:1 aqueous acetic acid solution at pH 9.0 – 9.5 at room temperature to give slurry. The slurry was filtered and dried to give 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide (8.2 g, 79%) as pure compound having melting point 265 - 267°C (from water).

Purity by HPLC: 99.73%

IR absorptions: ν_{max}/cm^{-1}: 3360m (-NH, 1° amine), 3264m (-NH, 2° amine), 3163m (-CH, aromatic), 1599m (-C-C, aromatic in ring), 1520m (-C-C, aromatic in ring), 1373m (-CH, alkane), 1317s (-C-N amine), 1185m (-C-N, aliphatic amine), 1163m (-C-N, aliphatic amine), 1150s (-S=O, sulfonamide), 850m (-C-Cl, halo comp)

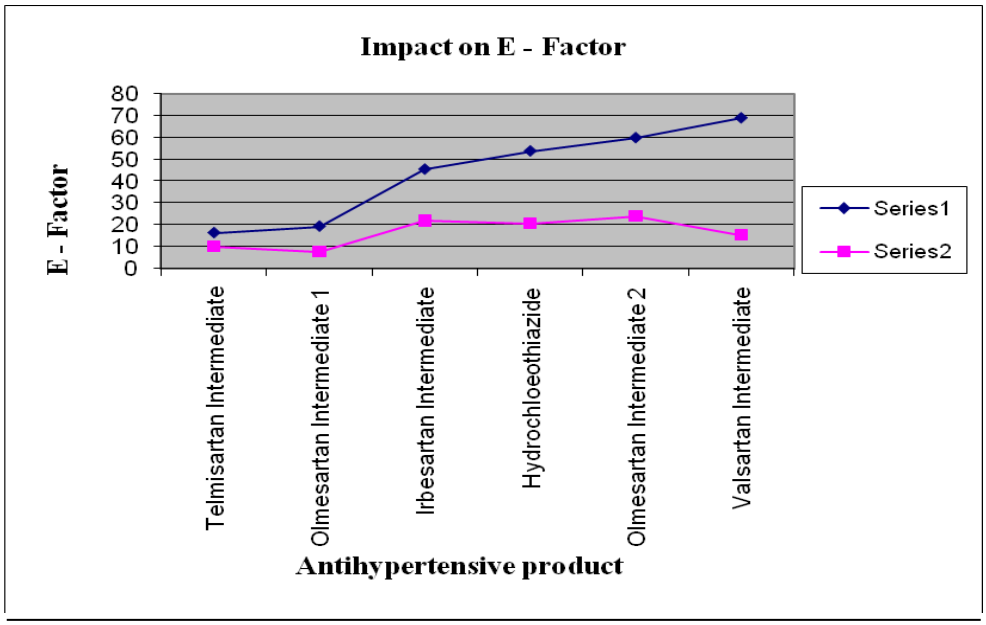
δ_H(400 MHz; DMSO) :

δ : 2.51 (1H, s, -NH, 2°amine), 3.42 (1H, s, -NH, 2°amine), 4.68 – 4.78 (2H, t, $-CH_2$), 6.98 (1H, s, Ar-H), 7.56 (2H, bs, $-NH_2$ or 1°amine), 7.99 (1H, s, Ar-H)

Mass: *m/z* 297 (M^+ 25%), 285 (58), 269 (75), 253 (2%), 246 (2), 232 (10), 218 (11), 205 (45), 188 (22), 154 (20), 139 (26), 125 (85), 108 (15), 90 (29).

3. RESULTS

Our investigations reflects the comparison between E-factors and % Yield of N-alkylation reactions of 2° amines **1** with substituted bromo methyl biaryl compounds **2** during the synthesis of different sartans intermediates **3** and API Hydrochlorothiazide both by conventional process as well as by catalytic amount of hydrotalcite as base. The outcomes of present research work is summarized in the below table 1 as the comparison of % yield and E factor based on available literature with products obtained using hydrotalcite we reported.



Series 1 -♦- : Trend of E-factor as per prior art or conventional process

Series 2 -□- : Trend of E-factor as per present novel research work

Figure 2

Impact on E – Factor by usage of Hydrotalcite

Table 1

% yield and E – Factor Summary as per present research work.

Product	Entry	% Yield		Calculation of E-Factor with Conventional Base	Observed E- Factor with usage of Hydro-talcite	% Reduction in E - Factor	Reference
		Reported with conventional Base	Achieved with Hydro-talcite				
Olmesartan Intermediate 1	**7**	80	83.2	19.26	7.74	40.19	19
Olmesartan Intermediate 2	**10**	88	87.7	59.92	23.98	40.00	
Irbesartan	**14**	87	88	45.47	21.87	48.09	22

Intermediate							
Telmisartan Intermediate	**18**	85	86	16.31	10.09	61.86	30
Valsartan Intermediate	**22**	90	91	69.00	15.35	22.24	38
Hydrochloro thiazide	**23**	46	79	53.80	20.72	38.51	42

4. DISCUSSION

However according to the present work, there is drastic reduction of E – factor with usage of recoverable Hydrotalcite as green catalyst and there is no any change in the % yield during the usage of it within the same molecular frame work.

Calculation of E – Factor

Table 2

Calculation as per Example of (*J. Med. Chem.* 1996, 39, 323 – 338) Olmesartan Intermediate 1[19]

	Name of Raw Material	Reported Qty.	Density	Reported Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	Imidazole derivative	5.00 g	--	5.00	0.42	0.42
2	TTBB	12.76 g	--	12.76	1.07	1.07
3	Potassium tert butoxide	2.33 g	--	2.33	0.20	0.20
4	Dimethyl acetamide	130 ml	0.94	0.94	0.08	0.08
5	Ethyl acetate 1	50 ml	0.897	44.85	3.76	3.76
6	Water	50 ml	1.00	50.00	4.19	4.19
7	Ethyl acetate 2	50 ml	0.897	44.85	3.76	3.76
8	Hexane	100 ml	0.69	69.00	5.78	5.78
	E - Factor					**19.26**
	Olmesartan Intermediate 1	11.93 g		11.93	**1.00**	

Table 3

Calculation as per present research work of Olmesartan Intermediate 1

	Name of Raw Material	Used Qty.	Density	Net used Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	Imidazole derivative	10.00 g	--	10.00	0.40	0.40
2	TTBB	24.58 g	--	24.58	0.99	0.99
3	Hydrotalcite	6.30 g	--	6.30	0.25	0.00
4	Dimethyl acetamide	50.00 ml	0.94	47.00	1.90	1.90
5	TBAB	1.19 g	--	1.19	0.05	0.05
6	Water 1	20.00 ml	1.000	20.00	0.81	0.81
7	Water 2	10.00 ml	1.000	10.00	0.40	0.40
8	Acetone	100.00 ml	0.791	79.10	3.19	3.19
	E - Factor					**7.74**
	Olmesartan Intermediate 1	24.80		24.80	1.00	

Table 4
Calculation as per Example of (*J. Med. Chem.* 1996, 39, 323 – 338) Olmesartan Intermediate 2[19]

	Name of Raw Material	Reported Qty.	Density	Reported Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	OLM I	30.00 g	--	30.00	1.02	1.02
2	$LiOH.H_2O$	2.65 g	--	2.65	0.09	0.09
3	Dioxane	344.00 ml	1.03	354.32	12.09	12.09
4	Water 1	158.00 ml	1.00	158.00	5.39	5.39
5	Ethyl acetate 1	600.00 ml	0.897	538.20	18.37	18.37
6	Sodium chloride	28.00 g	--	28.00	0.96	0.96
7	Sodium Sulphate	50.00 g	--	50.00	1.71	1.71
8	Dimethyl acetamide	176.00 ml	0.94	165.44	5.65	5.65
9	Potassium carbonate	6.08 g	--	6.08	0.21	0.21
10	DMDO -Cl	11.20 g	--	11.20	0.38	0.38
11	Ethyl acetate 2	150.00 ml	0.897	134.55	4.59	4.59
12	Water 2	150.00 ml	1.000	150.00	5.12	5.12
13	Magnesium Sulphate	30.00 g	--	30.00	1.02	1.02
14	Ethyl acetate 3	60.00 ml	0.897	53.82	1.84	1.84
15	Iso propyl Ether	60.00 ml	0.725	43.50	1.48	1.48
	E - Factor					**59.92**
	Olmesartan Intermediate 2	29.30 g		29.30	**1.00**	

Table 5
Calculation as per present research work of Olmesartan Intermediate 2

	Name of Raw Material	Used Qty.	Density	Net Used Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	OLM I	20.00 g	--	20.00	1.02	1.02
2	KOH	2.28 g	--	2.28	0.12	0.12
3	IPA	80.00 ml	0.786	62.88	3.21	3.21
4	Ethyl acetate 1	20.00 ml	0.897	17.94	0.92	0.92
5	Dimethyl acetammide	40.00 ml	0.94	37.60	1.92	1.92
6	Hydrotalcite	1.05 g	--	1.05	0.05	0.00
7	TBAB	1.00 g	--	1.00	0.05	0.05
8	DMDO-Cl	6.30 g	--	6.30	0.32	0.32
9	MDC	100.00 ml	1.33	133.00	6.79	6.79
10	Water 1	60.00 ml	1.00	60.00	3.06	3.06
11	Water 2	40.00 ml	1.00	40.00	2.04	2.04
12	Sodium Sulphate	10.00 g	--	10.00	0.51	0.51
13	Methanol	100.00 ml	0.791	79.10	4.04	4.04
14	**E - Factor**					**23.98**
	Olmesartan Intermediate 2	19.60	--	19.60	**1.00**	

Table 6
Calculation as per Example 5 (US 5270317) of Irbesartan Intermediate[22]

	Name of Raw Material	Reported Qty.	Density	Reported Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one	0.97 g	-	0.97	0.58	0.58
2	4-bromomethyl-2'-cyanobiphenyl	1.50 g	-	1.50	0.89	0.89
3	Sodium hydride (as an 80% dispersion in oil)	0.25 g	-	0.25	0.15	0.15
4	DMF	25.00 ml	0.95	23.75	14.14	14.14
5	Ethyl acetate 1	9.70 ml	0.897	8.70	5.18	5.18
6	water	9.70 ml	1.00	9.70	5.77	5.77
7	MDC	15.12 ml	1.33	20.11	11.97	11.97
8	Ethyl acetate 2	1.68 ml	0.897	1.51	0.90	0.90
9	Sodium Sulfate	0.19 g	-	0.19	0.12	0.12
10	Silica of Colum chromatography	9.70 g	-	9.70	5.77	5.77
	E - Factor					**45.47**
	Irbesartan Intermediate	1.66 g	--	1.66	**1.00**	

Table 7
Calculation as per present research work of Irbesartan Intermediate

	Name of Raw Material	Used Qty.	Density	Used Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one	5.00 g	--	5.00	0.57	0.57
2	4-bromomethyl-2'-cyanobiphenyl	5.66 g	--	5.66	0.65	0.65
3	Hydrotalcite	10.00 g	--	10.00	1.15	0.00
4	Acetonitrile	50.00 ml	0.786	39.30	4.50	4.50
5	MDC	50.00 ml	1.33	66.50	7.62	7.62
6	Water	50.00 ml	1.00	50.00	5.73	5.73
7	Sodium Sulfate	1.00 g	--	1.00	0.11	0.11
8	Cyclohexane	25.00 ml	0.779	19.48	2.23	2.23
9	Acetone	5.00 ml	0.791	3.96	0.45	0.45
	E - Factor					**21.87**
	Irbesartan Intermediate	8.73 g	--	8.73	**1.00**	

Table 8
Calculation as per Example of (OPRD Paper 2007, 11, 81 – 85) Telmisartan Intermediate[30]

	Name of Raw Material	Reported Qty.	Density	Reported Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	BIM	10.00 g	--	10.00	0.68	0.68
2	KOH Flacks	2.80 g	--	2.80	0.19	0.19
3	Bromomethyl biphenyl Methyl Ester	16.20 g	--	16.20	1.10	1.10
4	Acetone	120.00 ml	0.791	94.92	6.45	6.45
5	Methanol	50.00 ml	0.792	39.60	2.69	2.69
6	30 % Methanolic HCl	27.00 ml	0.791	21.36	1.45	1.45

7	Acetonitrile	70.00 ml	0.786	55.02	3.74	3.74
	E - Factor					**16.31**
	Telmisartan Intermediate	14.80 g	--	14.80	**1.00**	

Table 9
Calculation as per present research work of Telmisartan Intermediate

	Name of Raw Material	Used Qty.	Density	Used Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	BIM	4.50 g	--	4.50	0.67	0.67
2	Hydrotalcite	0.51 g	--	0.51	0.08	0.00
3	Bromomethyl biphenyl Methyl Ester	4.95 g	--	4.95	0.74	0.74
4	Acetone	40.00 ml	0.791	31.64	4.71	4.71
5	Acetonitrile	34.00 ml	0.786	26.72	3.98	3.98
6	**E - Factor**					**10.09**
	Telmisartan Intermediate	6.72		6.72	**1.00**	

Table 10
Calculation as per Example (1C, US 5399578 B2) of Valsartan Intermediate[38]

	Name of Raw Material	Reported Qty.	Density	Reported Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester	1.15 g	--	1.15	0.88	0.88
2	Triethylamine	0.63 ml	0.725	0.46	0.35	0.35
3	Diethyl ether	11.50 ml	0.713	8.20	6.31	6.31
4	Methylene dichloride	10.78 ml	1.33	14.34	11.03	11.03
5	Valeryl chloride	0.56 ml	1.016	0.57	0.44	0.44
6	Water	23.00 ml	1.00	23.00	17.69	17.69
7	Sodium bicarbonate	0.76 g	--	0.76	0.58	0.58
8	Sodium Chloride	2.88 g	--	2.88	2.22	2.22
9	Ethyl acetate	23.00 ml	0.897	20.63	15.87	15.87
10	Petroleum ether	23.00 ml	0.77	17.71	13.62	13.62
	E - Factor					**69.00**
	Valsartan Intermediate	1.30		1.30	**1.00**	

Table 11
Calculation as per present research work of Valsartan Intermediate

	Name of Raw Material	Used Qty.	Density	Used Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine	10.00 g	--	10.00	0.87	0.87

	methyl ester					
2	Hydrotalcite	2.80 g	--	2.80	0.24	0.00
3	tert butyl ammonium bromide	0.50 g	--	0.50	0.04	0.044
4	water	80.00 ml	1.00	80.00	6.97	6.97
5	Toluene	60.00 ml	0.867	52.02	4.54	4.535
6	Ethyl acetate	30.00 ml	0.897	26.91	2.35	2.35
7	Valeryl chloride	5.61 g	--	5.61	0.49	0.49
8	Sodium bicarbonate	1.00 g	--	1.00	0.09	0.087
	E - Factor					**15.35**
	Valsartan Intermediate 1	11.47 g	--	11.47	**1.00**	

Table 12
Calculation as per Example (1of US3163645 A) of Hydrochlorothiazide[42]

	Name of Raw Material	Reported Qty.	Density	Reported Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	5-chloro-2,4-disulfamyl-aniline	2.9 g	--	2.9	2.07	2.07
2	anhydrous diethyleneglycol dimethylether	15 ml	0.909	13.64	9.74	9.739
3	ethyl acetate + HCl solution	0.5 ml	0.897	0.45	0.32	0.32
4	Para formaldehyde	0.33 g	--	0.33	0.24	0.24
5	Water (Considerered 20 Vol)	58.00 ml	1.00	58.00	41.43	41.43
	E - Factor					**53.80**
	Hydrochlorothiazide	1.4 g	--	1.4	**1.00**	

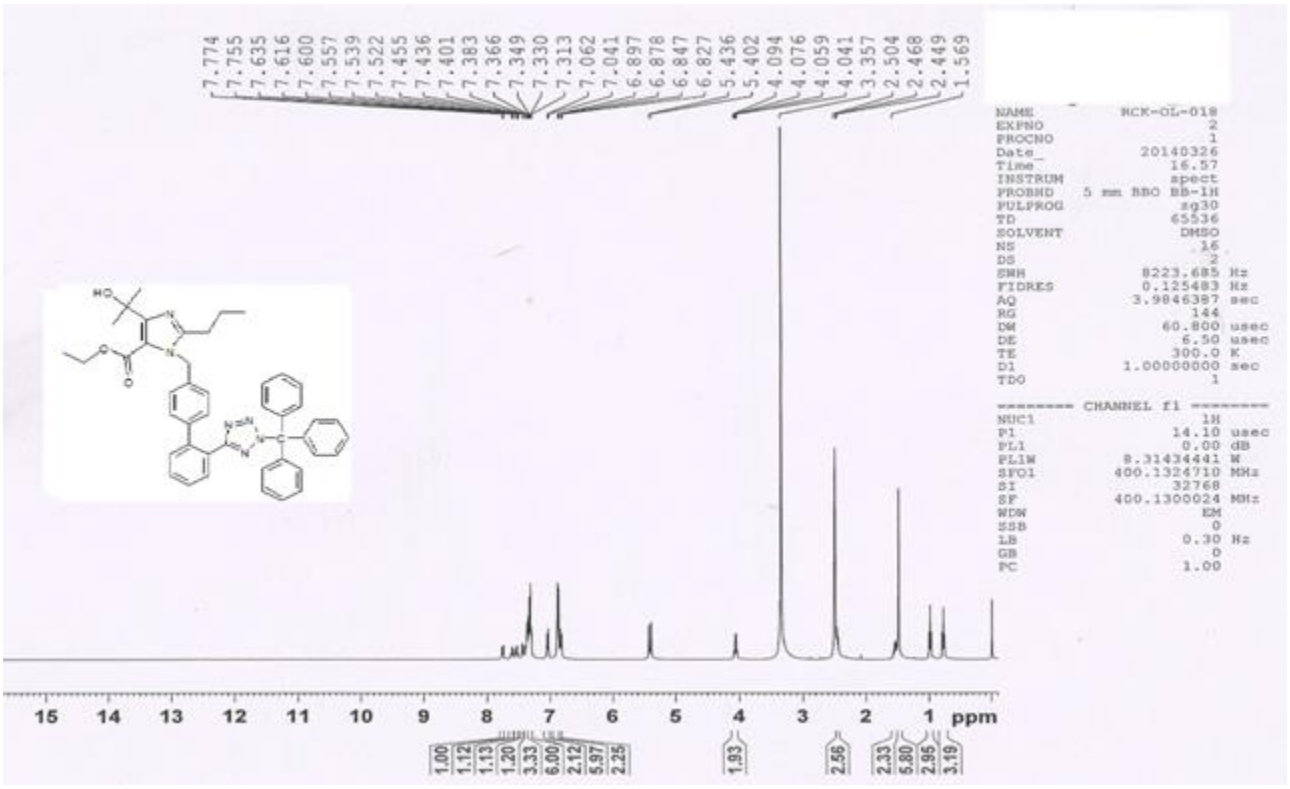
Table 13
Calculation as per present research work of Hydrochlorothiazide

	Name of Raw Material	Used Qty.	Density	Used Qty. (g)	Kg / 1 Kg	Net consumption Kg / 1 Kg
1	5-chloro-2,4-disulfamyl-aniline	10.00 g	--	10.00	1.22	1.22
2	Hydrotalcite	0.20 g	--	1.07	0.13	0.00
3	Paraformaldehyde	1.07 g	--	0.20	0.02	0.02
4	Water 1	100.00 ml	1.00	100.00	12.20	12.20
5	25 % Ammonia solution	30.00 ml	0.91	27.30	3.33	3.33
6	Water 2	20.00 ml	1.00	20.00	2.44	2.44
7	Acetic acid	6.25 ml	0.95	5.94	0.72	0.72
8	Water 2	6.25 ml	1.00	6.25	0.76	0.76
9	Charcoal	0.20 g	--	0.20	0.02	0.02
	E - Factor					**20.72**
	Hydrochlorothiazide	8.20		8.20	**1.00**	

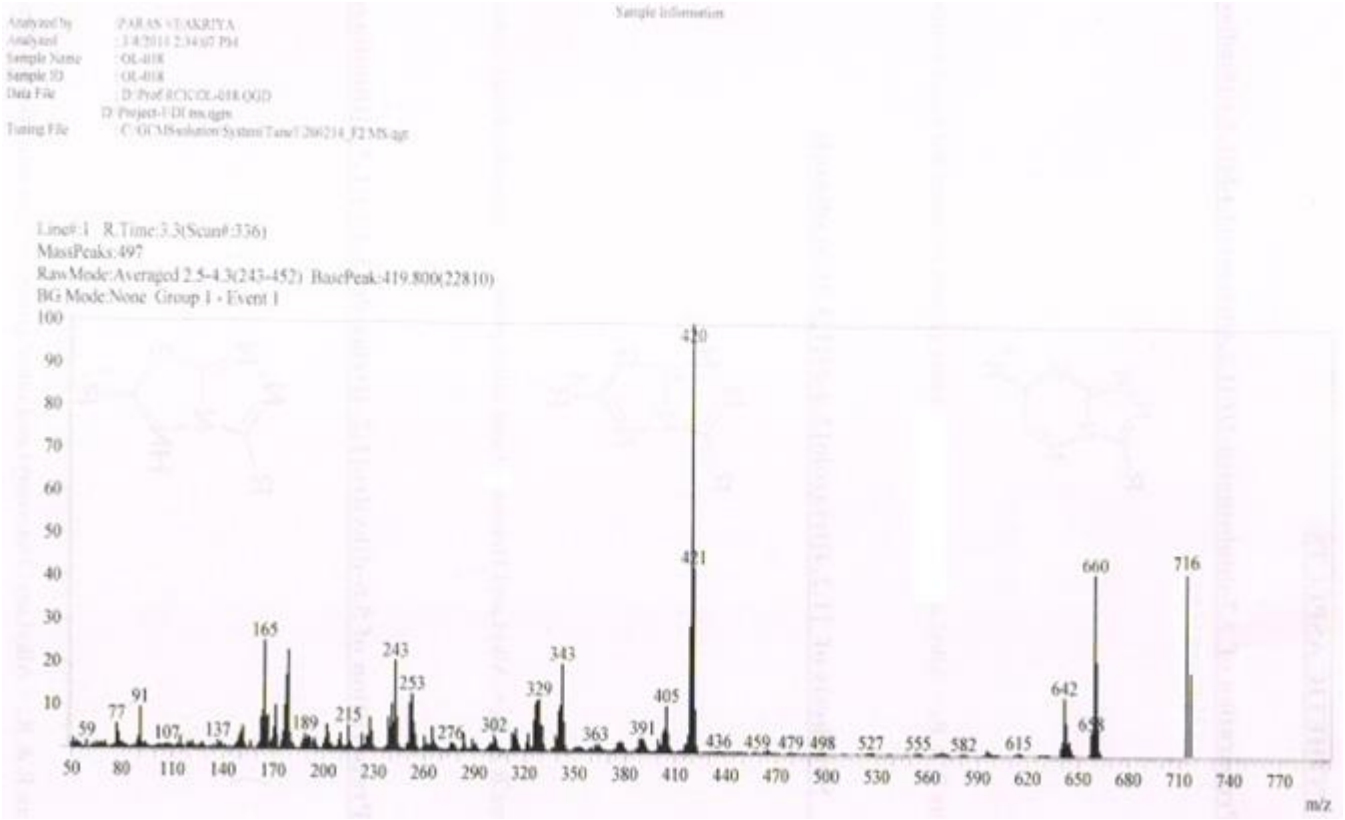
Figure 3

Spectra of compound 7 (Olmesartan Intermediate 1)

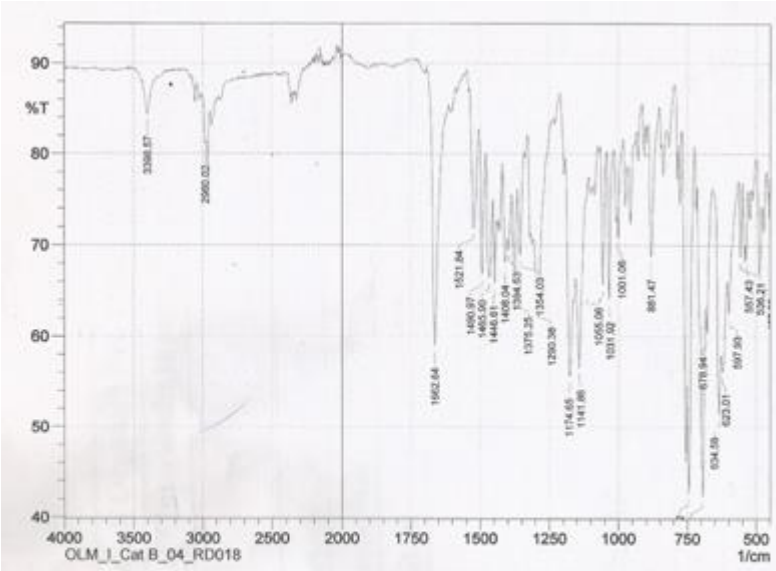
3.1. [1]HNMR of compound 7 (Olmesartan Intermediate 1) 400 MHz (DMSO)



3.2. Mass spectrum of compound 7 (Olmesartan Intermediate 1)



3.3. IR Absorption Spectra of compound 7 (Olmesartan Intermediate 1)



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OLM_I_Cat B_04_RD018

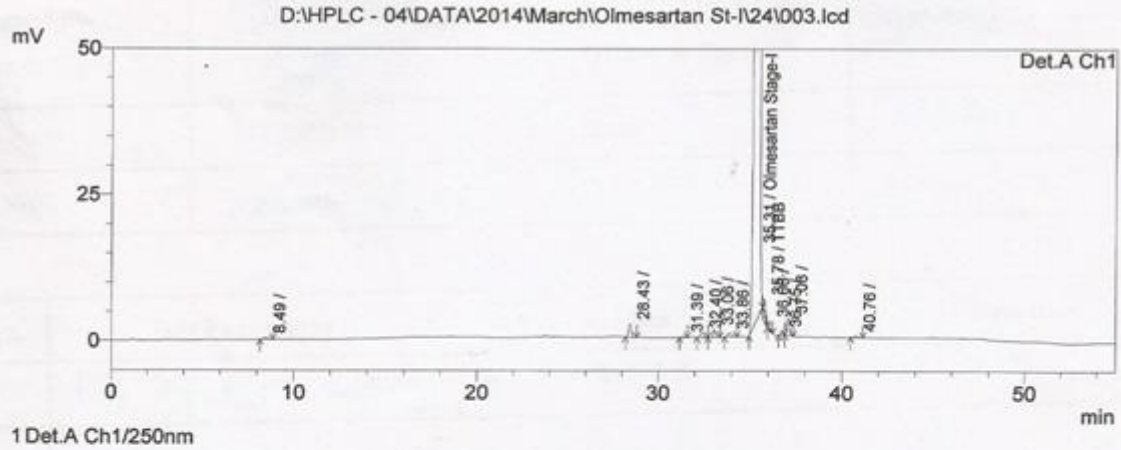
Date/Time;3/26/201412:18:14 PM
No. of Scans; 20
Resolution; 4 (1/Cm)
Apodization; Happ-Genzel
User; FTIR

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	487.99	66.73	9.888	495.71	480.28	2.313	0.496
2	536.21	68.461	3.878	540.07	530.42	1.4	0.107
3	557.43	68.697	8.218	563.21	549.71	1.815	0.274
4	597.93	62.513	5.064	603.72	565.14	5.809	0.232
5	623.01	56.192	3.232	626.87	605.65	4.695	0.328
6	634.58	51.374	9.852	657.73	628.79	5.598	0.643
7	678.94	60.277	4.989	682.8	659.66	3.707	0.183
8	694.37	42.309	24.849	713.66	684.73	7.459	2.734
9	744.52	42.728	17.841	750.31	725.23	5.526	1.282
10	881.47	68.762	14.942	891.11	852.54	4.183	1.306
11	1001.06	70.821	3.786	1004.91	983.7	2.457	0.076
12	1031.92	64.084	15.901	1039.63	1018.41	2.885	0.844
13	1055.06	65.684	14.952	1064.71	1041.56	3.077	0.906
14	1141.86	56.583	12.534	1153.43	1107.14	7.934	1.311
15	1174.65	55.603	14.974	1190.08	1163.08	5.491	1.427
16	1290.38	63.446	10.445	1305.81	1244.09	8.396	1.407
17	1354.03	68.921	8.937	1363.67	1342.46	2.818	0.549
18	1375.25	64.632	11.06	1384.89	1365.6	2.954	0.623
19	1394.53	69.51	2.698	1398.39	1386.82	1.65	0.094
20	1408.04	68.115	6.261	1417.68	1400.32	2.6	0.357
21	1446.61	65.889	7.631	1452.4	1440.83	1.833	0.27
22	1465.9	66.475	10.778	1477.47	1454.33	3.578	0.948
23	1490.97	66.826	14.438	1502.55	1479.4	2.958	0.855
24	1521.84	71.887	13.322	1537.27	1502.55	3.74	1.278
25	1662.64	59	27.424	1691.57	1631.78	7.347	3.474
26	2980.02	81.131	1.451	2999.31	2974.23	1.969	0.057
27	3398.57	84.361	3.421	3437.15	3363.86	4.736	0.591

3.4. HPLC Purity of compound 7 (Olmesartan Intermediate 1)

Acquired by	: Admin
Sample Name	: Olmesartan Stage-I
Sample ID	: OLM/I/CAT B/04/RD018
Injection Volume	: 10 uL
Vail #	: 3
Data Filename	: D:\HPLC - 04\DATA\2014\March\Olmesartan St-I\24\003.lcd
Method Filename	: D:\HPLC - 04\METHOD\Olmesartan Medoxomil (Stage-I).lcm
Date Acquired	: 3/24/2014 6:35:52 PM
Data Processed	: 3/25/2014 12:51:47 AM
Description	: Purity,Symmetry C8(ADL/COL/056)

<Chromatogram>



1 Det.A Ch1/250nm

<Results>

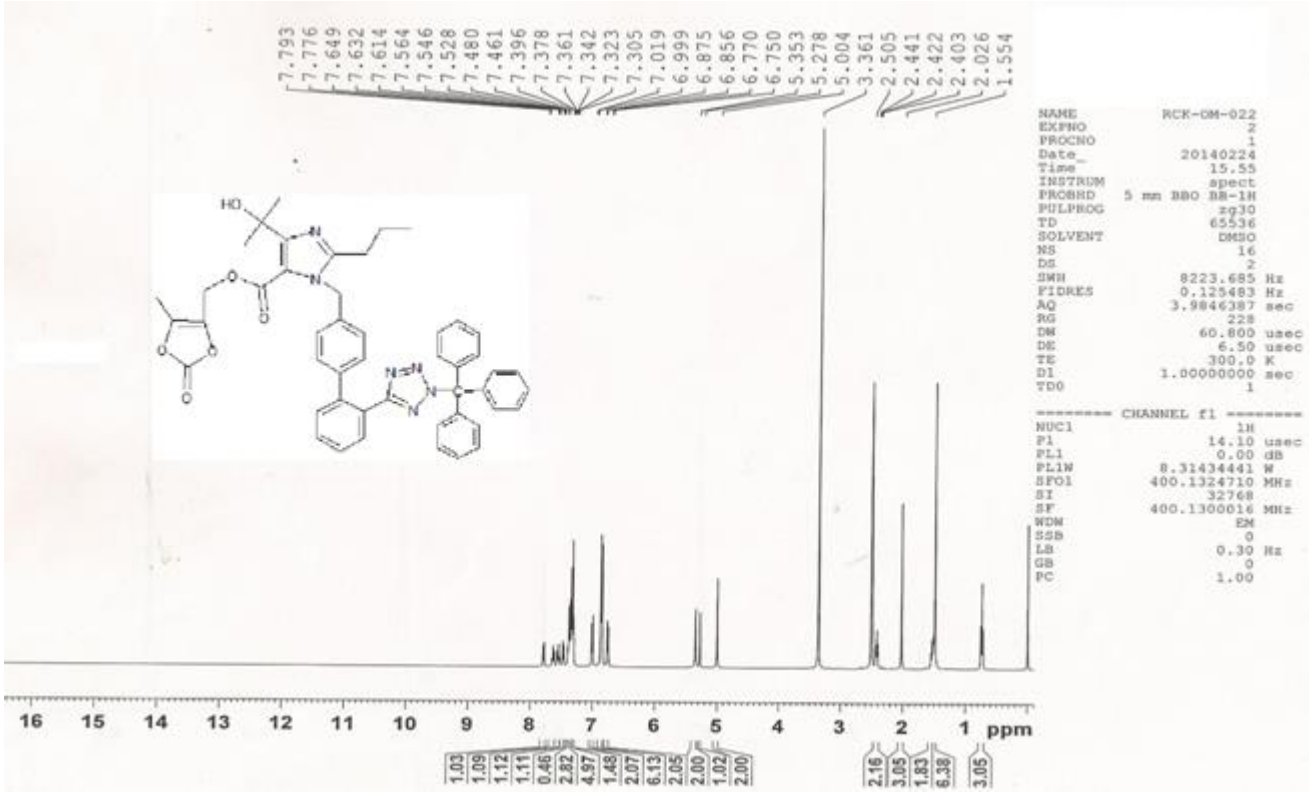
Detector A Ch1 250nm

Peak#	Name	Ret. Time	Area	Area %	RRT
1		8.49	5323	0.03	0.24
2		28.43	23491	0.12	0.81
3		31.39	2364	0.01	0.89
4		32.40	11027	0.06	0.92
5		33.06	11955	0.06	0.94
6		33.86	11377	0.06	0.96
7	Olmesartan Stage-I	35.31	19659459	99.32	1.00
8	TTBB	35.78	18970	0.10	1.01
9		36.06	11544	0.06	1.02
10		36.75	5015	0.03	1.04
11		37.08	28992	0.15	1.05
12		40.76	4074	0.02	1.15
Total			19793591	100.00	

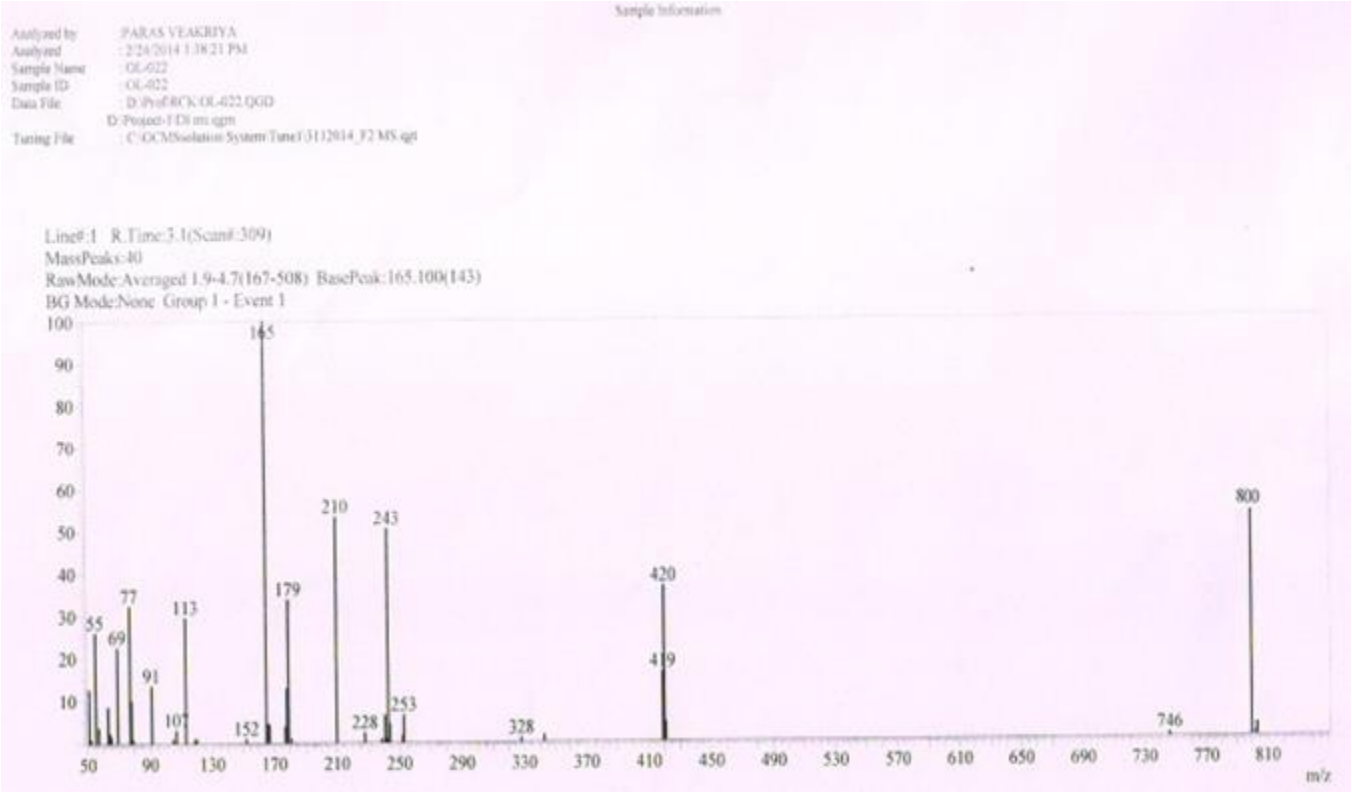
Figure 4

Spectra of compound 10 (Olmesartan Intermediate 2)

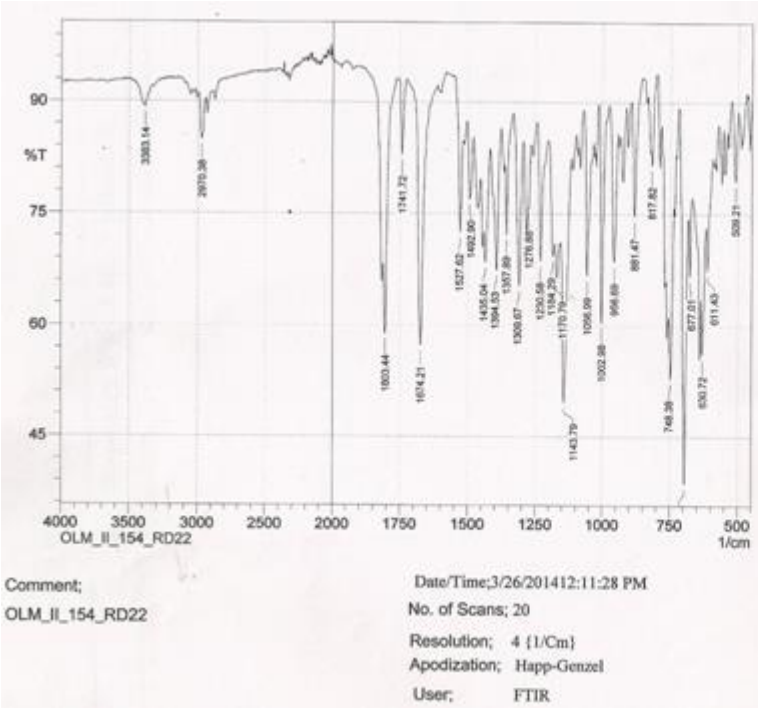
4.1. [1]HNMR of compound 10 (Olmesartan Intermediate 2) 400 MHz (DMSO)



4.2. Mass spectrum of compound 10 (Olmesartan Intermediate 2)



4.3. IR Absorption Spectra of compound 10 (Olmesartan Intermediate 2)



	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	509.21	79.385	10.023	522.71	499.56	1.709	0.597
2	611.43	67.462	6.614	615.29	592.15	2.789	0.265
3	630.72	56.201	8.349	634.58	617.22	3.361	0.465
4	677.01	66.699	8.609	680.87	671.23	1.422	0.261
5	696.3	38.676	41.435	717.52	682.8	7.359	4.185
6	748.38	52.92	14.16	756.1	736.81	4.164	1.043
7	817.82	81.572	3.843	821.68	800.46	1.19	0.073
8	881.47	74.661	16.526	894.97	854.47	2.684	1.163
9	956.69	68.639	18.693	975.98	943.19	3.464	1.567
10	1002.98	80.454	28.338	1014.56	987.55	3.248	1.824
11	1056.99	66.768	20.57	1070.49	1033.85	3.885	1.598
12	1143.79	49.69	24.867	1155.36	1116.78	7.422	3.015
13	1170.79	66.227	4.663	1176.58	1157.29	3.141	0.266
14	1184.29	69.342	5.161	1201.65	1178.51	2.87	0.299
15	1230.58	68.745	17.705	1244.09	1203.58	4.075	1.417
16	1276.88	75.623	1.587	1278.81	1267.23	1.177	0.05
17	1309.67	65.38	20.713	1332.81	1296.16	4.199	1.887
18	1357.89	72.188	10.595	1363.67	1332.81	2.565	0.373
19	1394.53	67.473	17.633	1417.68	1379.1	4.431	1.693
20	1435.04	68.492	7.021	1440.83	1419.61	2.728	0.468
21	1492.9	76.951	9.498	1504.48	1479.4	2.191	0.594
22	1527.62	72.499	15.04	1552.7	1516.05	2.704	0.861
23	1674.21	57.35	33.545	1724.36	1641.42	7.393	4.078
24	1741.72	82.908	10.181	1755.22	1726.29	1.42	0.52
25	1803.44	58.941	13.48	1811.16	1764.87	4.26	0.651
26	2970.38	84.881	5.949	2993.52	2941.44	2.916	0.73
27	3383.14	89.242	0.788	3394.72	3363.86	1.437	0.053

4.4. HPLC Purity of compound 10 (Olmesartan Intermediate 2)

Acquired by	: Admin
Sample Name	: OLM/II/Cat-B/031/RD022_Inj-02
Sample ID	: Olmesartan Stage-II
Injection Volume	: 10 uL
Data Filename	: D:\HPLC-08\Data\2014\March\Olmesartan\Stage-II\24\006.lcd
Method Filename	: D:\HPLC-08\Method\Olmesartan RS.lcm
Data Acquired	: 3/24/20145:40:54 PM
Data Processed	: 3/24/20148:44:54 PM
Description	: Test:RS Column ID No:ADL/COL/176

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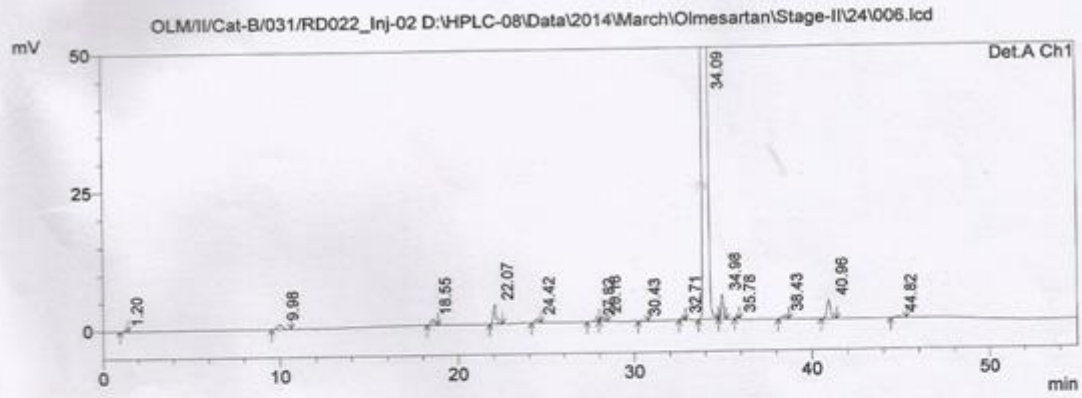


1 Det.A Ch1/250nm

<Results>

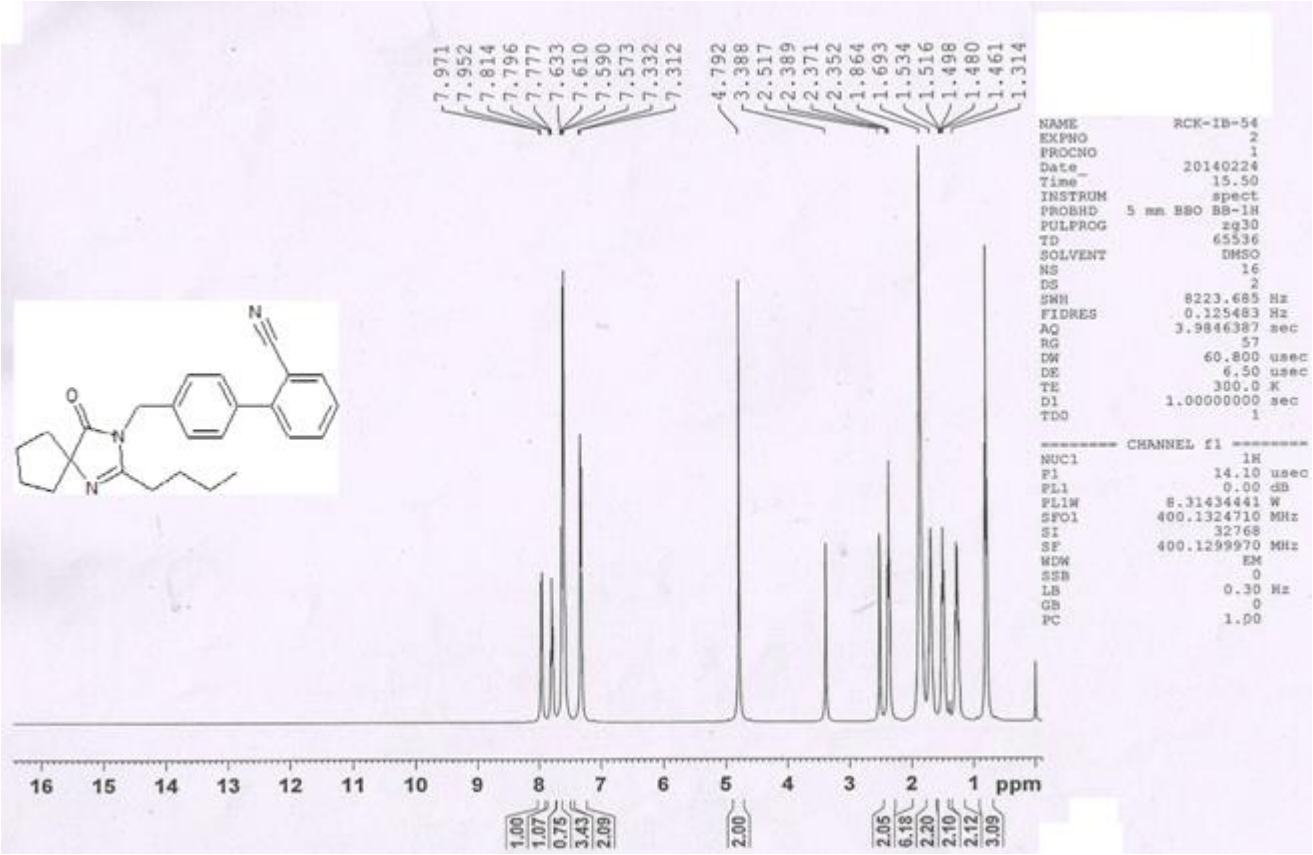
Detector A Ch1 250nm

Peak#	Name	Ret. Time	Area	Area %	RRT
1		1.20	1714	0.01	0.04
2		9.98	17968	0.10	0.29
3		18.55	12658	0.07	0.54
4		22.07	39209	0.22	0.65
5	K Salt	24.42	6458	0.04	0.72
6		27.82	2434	0.01	0.82
7		28.18	6611	0.04	0.83
8		30.43	1973	0.01	0.89
9		32.71	4579	0.03	0.96
10	Olmesartan Medoxomil	34.09	17914678	98.90	1.00
11		34.98	42956	0.24	1.03
12		35.78	2619	0.01	1.05
13		38.43	7903	0.04	1.13
14		40.96	47834	0.26	1.20
15		44.82	4550	0.03	1.31
Total			18114143	100.00	

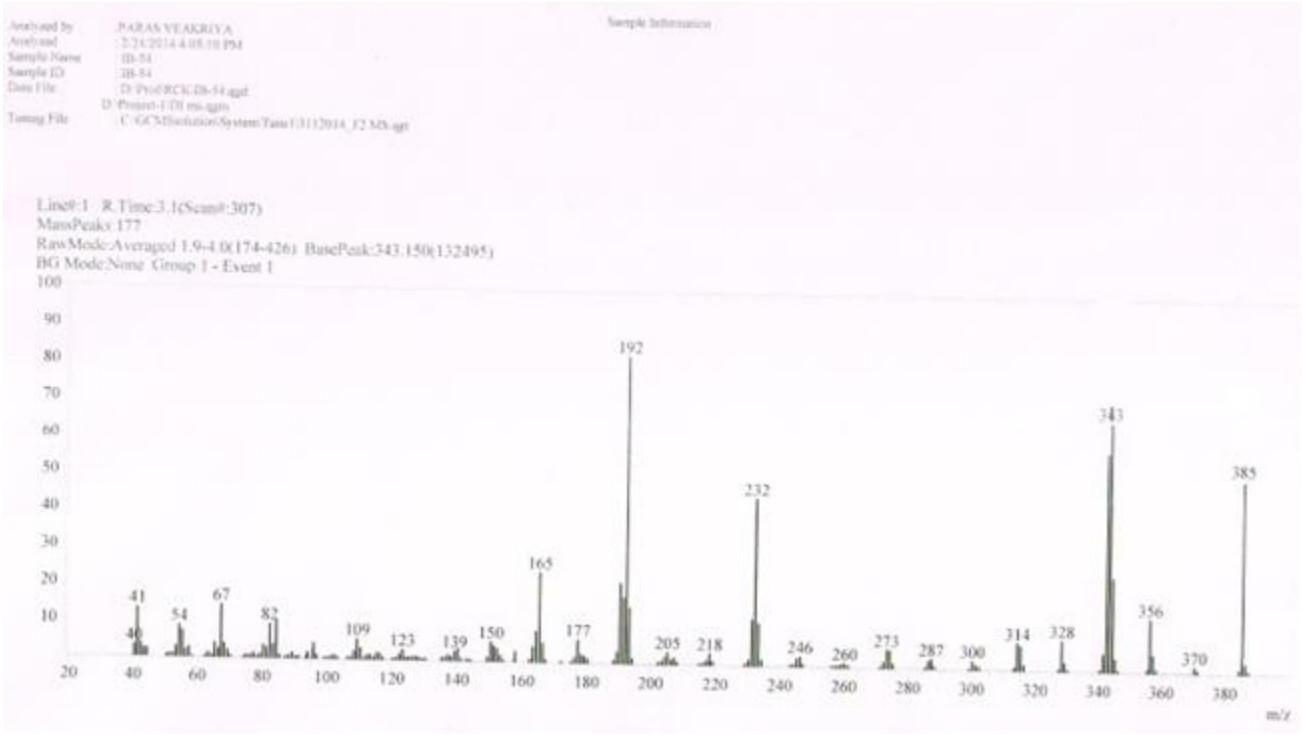
Figure 5

Spectra of compound 14 (Irbesartan Intermediate)

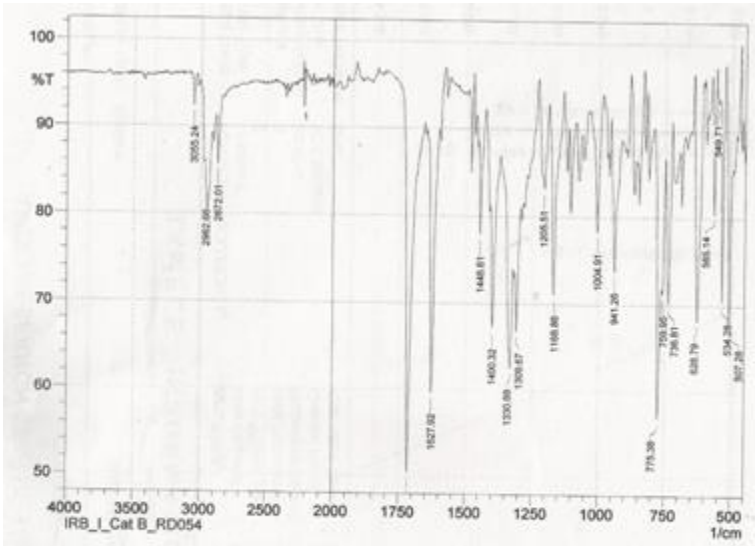
5.1. [1]H NMR of compound 14 (Irbesartan Intermediate) 400 MHz (DMSO)



5.2. Mass Spectrum of compound 14 (Irbesartan Intermediate)



5.3. IR Absorption Spectra of compound 14 (Irbesartan Intermediate)



	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	507.28	67.442	20.712	524.64	499.56	2.1	0.917
2	534.28	70.408	25.675	545.85	526.57	1.272	0.918
3	549.71	93.207	1.553	559.36	545.85	0.353	0.084
4	565.14	80.477	16.567	576.72	559.36	0.869	0.63
5	628.79	68.202	27.849	642.3	609.51	3.274	2.69
6	736.81	70.193	18.544	748.38	725.23	2.562	1.379
7	759.95	71.266	4.895	763.81	750.31	1.494	0.191
8	775.38	56.864	22.83	790.81	763.81	3.982	1.357
9	941.26	73.848	16.675	956.69	914.26	3.493	1.572
10	1004.91	78.337	14.953	1031.92	985.62	2.673	1.239
11	1168.86	71.155	22.262	1190.08	1136.07	3.957	2.394
12	1205.51	83.209	3.766	1211.3	1190.08	1.311	0.212
13	1309.67	66.801	8.917	1315.45	1296.16	2.649	0.506
14	1330.88	62.577	4.865	1334.74	1323.17	1.988	0.178
15	1400.32	67.272	15.153	1408.04	1373.32	3.757	1.136
16	1446.61	77.892	11.771	1454.33	1427.32	1.732	0.552
17	1627.92	59.651	29.847	1647.21	1602.85	4.645	2.521
18	1716.65	50.455	42.969	1764.87	1658.78	9.245	5.955
19	2872.01	85.644	6.353	2889.37	2839.22	2.279	0.538
20	2962.66	82.807	0.943	2972.31	2958.8	1.022	0.029
21	3055.24	92.29	3.605	3074.53	3037.89	0.873	0.206

Comment;
IRB_I_Cat B_RD054

Date/Time;3/26/201412:34:58 PM
No. of Scans;
Resolution; 4 {1/Cm}
Apodization; Happ-Genzel
User; FTIR

5.4. HPLC Purity of compound 14 (Irbesartan Intermediate)

Acquired by	: Admin
Sample Name	: Irbesartan
Sample ID	: IRB/I/CAT B/04/RD054
Injection Volume	: 10 uL
Vail #	: 4
Data Filename	: D:\HPLC - 04\DATA\2014\March\Olmesartan St-I\24\004.lcd
Method Filename	: D:\HPLC - 04\METHOD\Olmesartan Medoxomil (Stage-I).lcm
Date Acquired	: 3/24/2014 7:31:32 PM
Data Processed	: 3/25/2014 1:38:44 PM
Description	: Purity,Symmetry C8(ADL/COL/056)

<Chromatogram>

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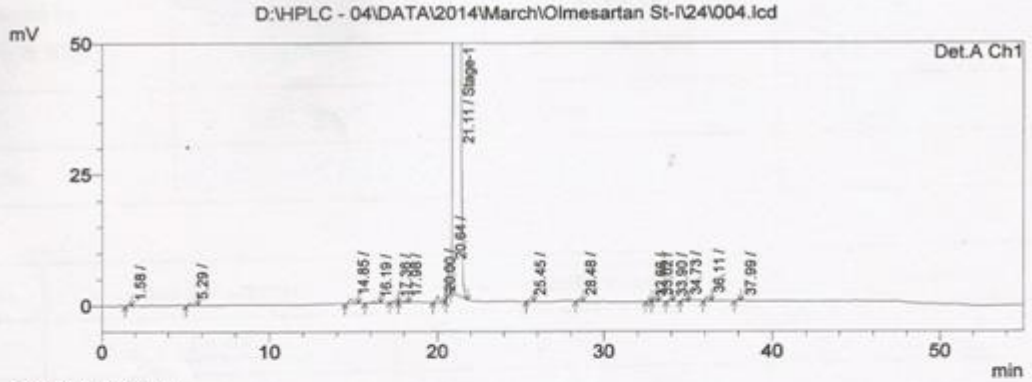


1 Det.A Ch1/250nm

<Results>

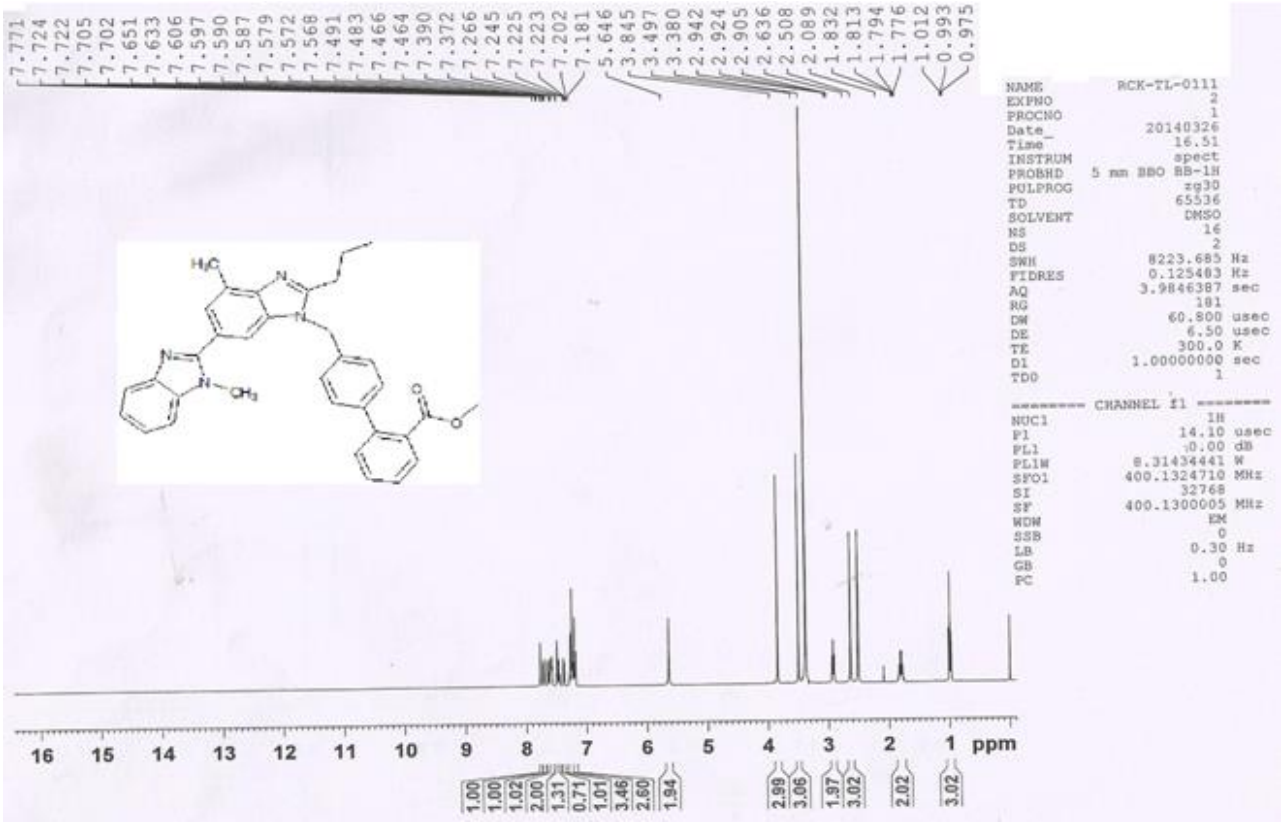
Detector A Ch1 250nm

Peak#	Name	Ret. Time	Area	Area %	RRT
1		1.58	2755	0.01	0.07
2		5.29	5945	0.03	0.25
3		14.85	14762	0.07	0.70
4		16.19	4255	0.02	0.77
5		17.36	3491	0.02	0.82
6		17.98	4101	0.02	0.85
7		20.00	15646	0.07	0.95
8		20.64	47041	0.21	0.98
9	Stage-1	21.11	21884196	99.42	1.00
10		25.45	3150	0.01	1.21
11		28.48	3700	0.02	1.35
12		32.66	2185	0.01	1.55
13		33.02	3810	0.02	1.56
14		33.90	2445	0.01	1.61
15		34.73	5613	0.03	1.65
16		36.11	6962	0.03	1.71
17		37.99	2358	0.01	1.80
Total			22012415	100.00	

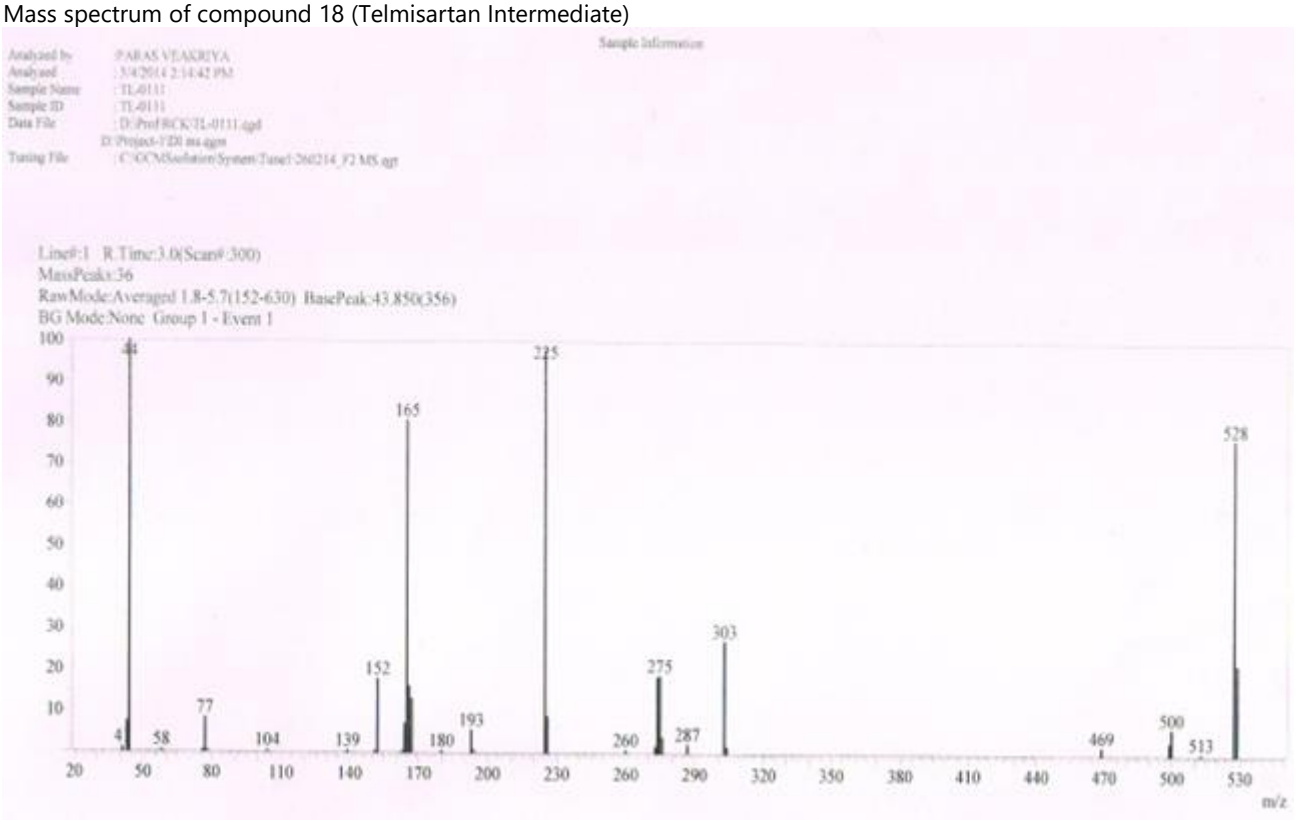
Figure 6

Spectra of compound 18 (Telmisartan Intermediate)

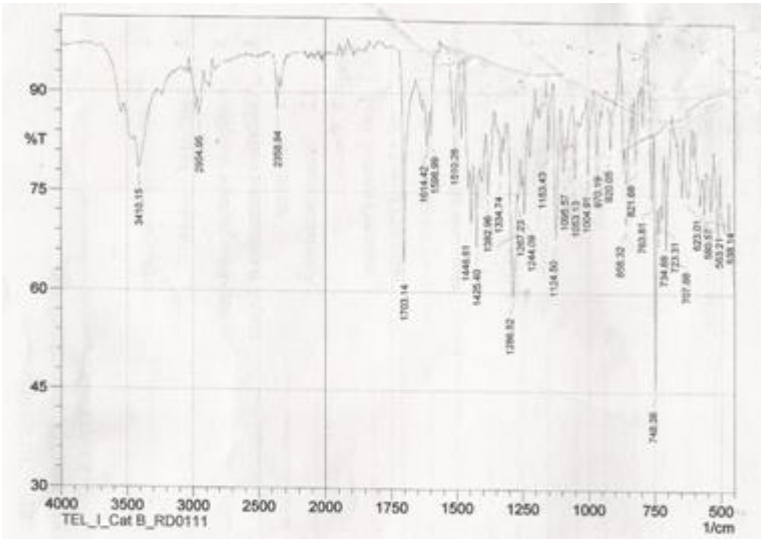
6.1. [1]HNMR of compound 18 (Telmisartan Intermediate) 400 MHz (DMSO)



6.2. Mass spectrum of compound 18 (Telmisartan Intermediate)



6.3. IR Absorption Spectra of compound 18 (Telmisartan Intermediate)



Comment;
TEL_I_Cat B_RD0111

Date/Time;3/26/201412:49:39 PM
No. of Scans;
Resolution; 4 {1/Cm}
Apodization; Happ-Genzel
User; FTIR

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	451.34	61.371	1.865	459.06	449.41	1.92	0.058
2	480.26	68.276	1.759	482.3	470.63	1.757	0.111
3	913.07	68.324	11.003	930.57	904.25	2.773	0.672
4	538.14	72.716	6.729	545.86	528.5	2.1	0.402
5	563.21	72.047	5.897	569	559.36	1.213	0.169
6	580.57	73.372	3.994	584.43	570.93	1.634	0.135
7	623.01	74.661	10.078	642.3	611.43	3.357	1.117
8	707.88	66.627	15.435	713.66	686.66	3.006	0.992
9	723.31	71.272	4.467	727.16	715.59	1.409	0.136
10	734.88	69.164	3.62	738.74	729.09	1.426	0.109
11	748.38	45.384	33.828	754.17	740.67	2.984	1.483
12	763.81	74.152	13.611	781.17	756.1	1.646	0.509
13	821.68	79.662	10.571	831.32	810.1	1.456	0.514
14	858.32	70.483	12.316	864.11	840.96	2.208	0.573
15	920.05	81.812	6.121	923.9	902.69	1.339	0.234
16	970.19	80.995	8.302	983.7	958.62	1.751	0.53
17	1004.91	77.969	12.508	1008.77	983.7	1.655	0.585
18	1053.13	77.291	9.941	1062.78	1045.42	1.402	0.382
19	1095.57	78.277	5.836	1109.07	1089.78	1.51	0.167
20	1124.5	68.21	22.19	1136.07	1109.07	2.903	1.658
21	1153.43	81.542	10.767	1163.08	1136.07	1.461	0.519
22	1244.09	72.039	8.289	1249.87	1232.51	1.914	0.416
23	1267.23	74.269	2.605	1271.09	1261.45	1.13	0.078
24	1286.52	59.359	19.572	1313.52	1271.09	6.274	2.19
25	1334.74	77.772	6.247	1342.46	1327.03	1.408	0.241
26	1382.96	74.869	9.116	1388.75	1359.82	2.722	0.705
27	1425.4	66.738	10.543	1431.18	1415.75	2.103	0.416
28	1446.61	70.469	8.252	1452.4	1438.9	1.674	0.281
29	1510.26	84.898	5.198	1517.98	1492.9	1.233	0.256
30	1598.99	83.572	6.213	1604.77	1581.63	0.988	0.161
31	1614.42	82.214	5.869	1627.92	1604.77	1.564	0.305
32	1703.14	64.396	31.105	1720.5	1658.78	4.289	2.745
33	2358.94	87.293	6.171	2387.87	2347.37	1.549	0.484
34	2954.95	86.363	3.689	2964.59	2916.37	2.377	0.445
35	3410.15	78.331	5.795	3437.15	3294.42	10.956	1.741

6.4. HPLC Purity of compound 18 (Telmisartan Intermediate)

Acquired by : Admin
Sample Name : Telmisartan
Sample ID : TEL/I/CAT B/05/RD0111
Vial : 3
Injection Volume : 10 uL
Data Filename : D:\HPLC-05\Data\2014\March\Telmisartan\25\005.lcd
Method Filename : D:\HPLC-05\Method\Telmisartan USP.lcm
Date Acquired : 3/25/2014 6:36:06 PM
Data Processed : 3/25/2014 8:38:50 PM
Description : WS/1M/TEL/001(TBB/S-1/1106B/RD25)
Test: RS, Column ID No.:ADL/COL/048

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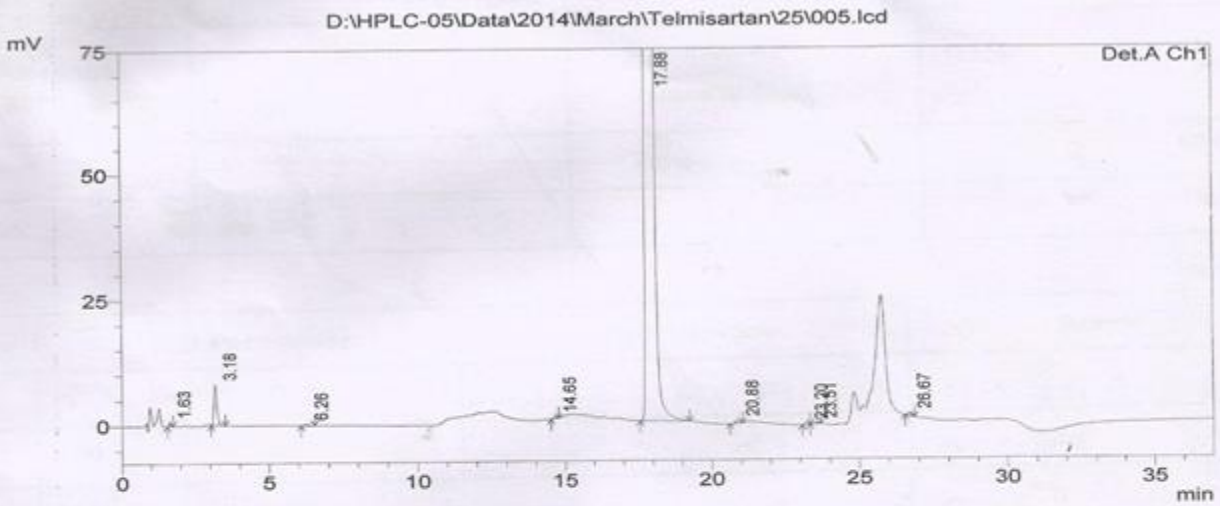


1 Det.A Ch1/230nm

<Results>

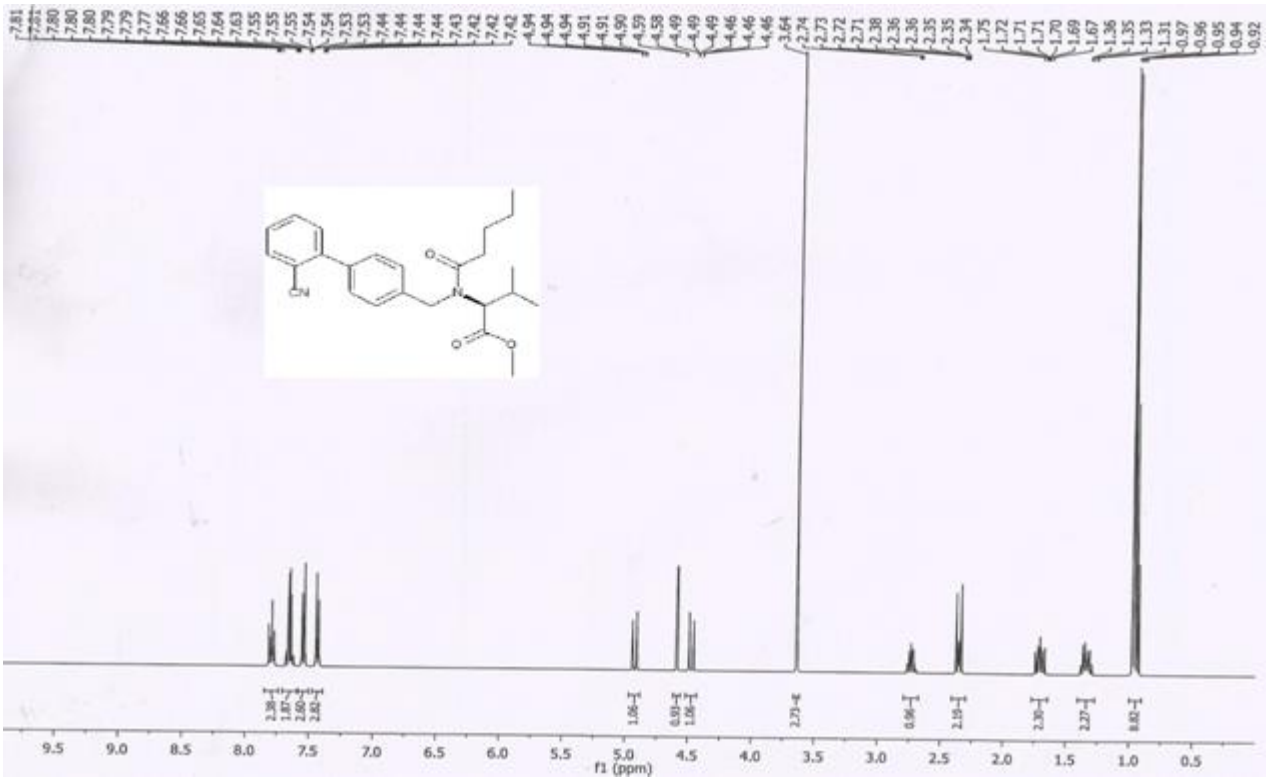
Detector A Ch1 230nm

Peak#	Name	Ret. Time	Area	Area %	RRT
1		1.63	3525	0.02	0.09
2		3.18	57701	0.38	0.18
3		6.26	2551	0.02	0.35
4		14.65	3205	0.02	0.82
5	Telmisartan stage-I	17.88	15281782	99.46	1.00
6		20.88	5912	0.04	1.17
7		23.20	1546	0.01	1.30
8		23.51	3244	0.02	1.31
9		26.67	4949	0.03	1.49
Total			15364415	100.00	

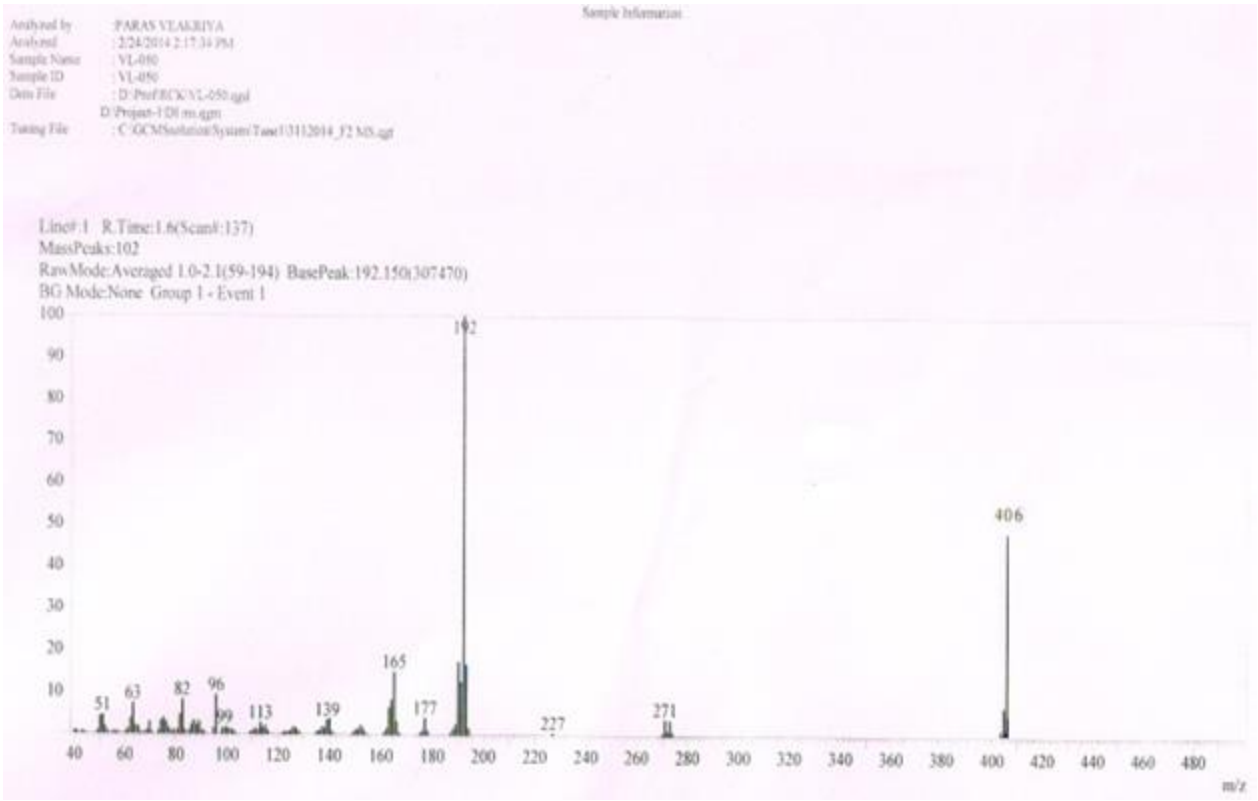
Figure 7

Spectra of compound 22 (Valsartan Intermediate)

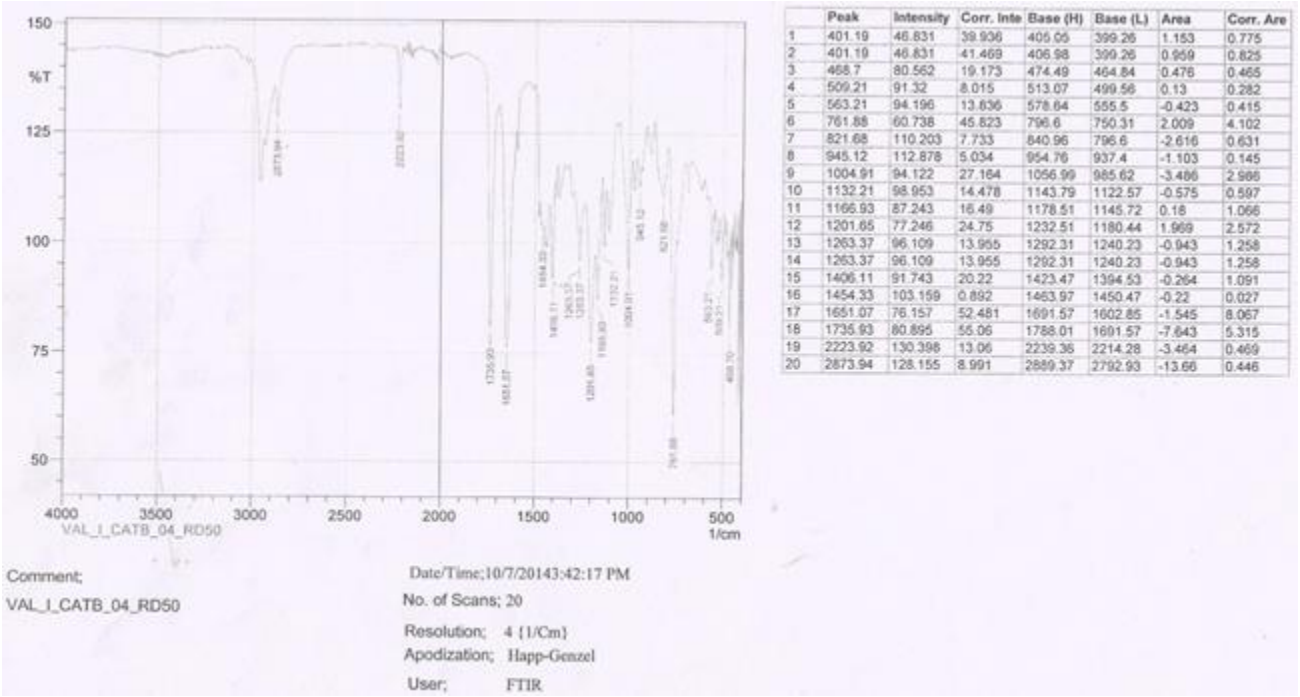
7.1. ^{1}H NMR of compound 22 (Valsartan Intermediate) 400 MHz (DMSO)



7.2. Mass Spectrum of compound 22 (Valsartan Intermediate)



7.3. IR Absorption Spectra of compound 22 (Valsartan Intermediate)

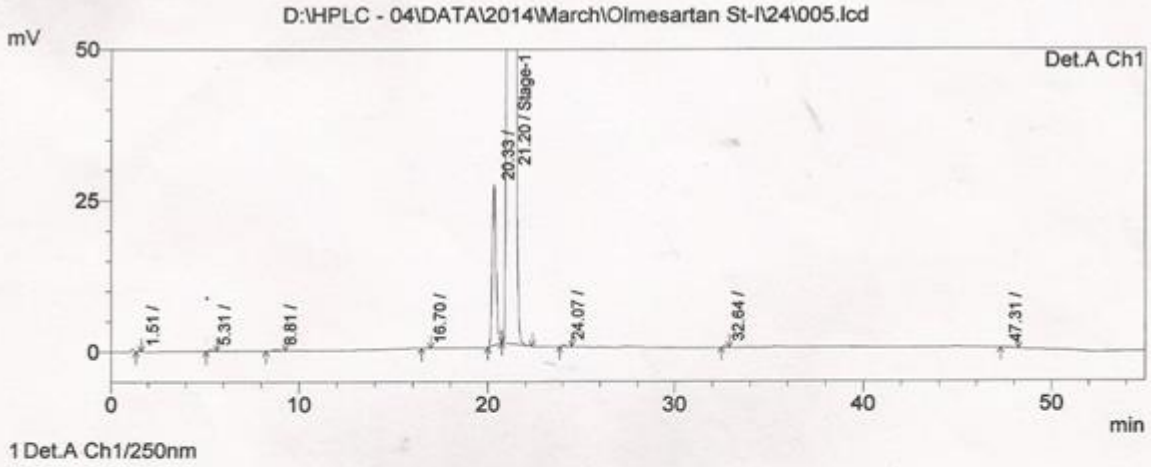


	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	401.19	46.831	39.936	405.05	399.26	1.153	0.775
2	401.19	46.831	41.469	406.98	399.26	0.959	0.825
3	468.7	80.562	19.173	474.49	464.84	0.476	0.465
4	509.21	91.32	8.015	513.07	499.56	0.13	0.282
5	563.21	94.196	13.836	578.64	555.5	-0.423	0.415
6	761.88	60.738	45.823	796.6	750.31	2.009	4.102
7	821.68	110.203	7.733	840.96	796.6	-2.616	0.631
8	945.12	112.878	5.034	954.76	937.4	-1.103	0.145
9	1004.91	94.122	27.164	1056.99	985.62	-3.486	2.986
10	1132.21	98.953	14.478	1143.79	1122.57	-0.575	0.597
11	1166.93	87.243	16.49	1178.51	1145.72	0.18	1.066
12	1201.65	77.246	24.75	1232.51	1180.44	1.969	2.572
13	1263.37	96.109	13.955	1292.31	1240.23	-0.943	1.258
14	1263.37	96.109	13.955	1292.31	1240.23	-0.943	1.258
15	1406.11	91.743	20.22	1423.47	1394.53	-0.264	1.091
16	1454.33	103.159	0.892	1463.97	1450.47	-0.22	0.027
17	1651.07	76.157	52.481	1691.57	1602.85	-1.545	8.057
18	1735.93	80.895	55.06	1788.01	1691.57	-7.643	5.315
19	2223.92	130.398	13.06	2239.36	2214.28	-3.464	0.469
20	2873.94	128.155	8.991	2889.37	2792.93	-13.66	0.446

7.4. HPLC Purity of compound 22 (Valsartan Intermediate)

Acquired by	: Admin
Sample Name	: Valsartan
Sample ID	: VAL/I/CAT B/04/RD050
Injection Volume	: 10 uL
Vail #	: 5
Data Filename	: D:\HPLC - 04\DATA\2014\March\Olmesartan St-I\24\005.lcd
Method Filename	: D:\HPLC - 04\METHOD\Olmesartan Medoxomil (Stage-I).lcm
Date Acquired	: 3/24/2014 8:27:12 PM
Data Processed	: 3/25/2014 1:39:35 PM
Description	: Purity,Symmetry C8(ADL/COL/056)

<Chromatogram>



1 Det.A Ch1/250nm

<Results>

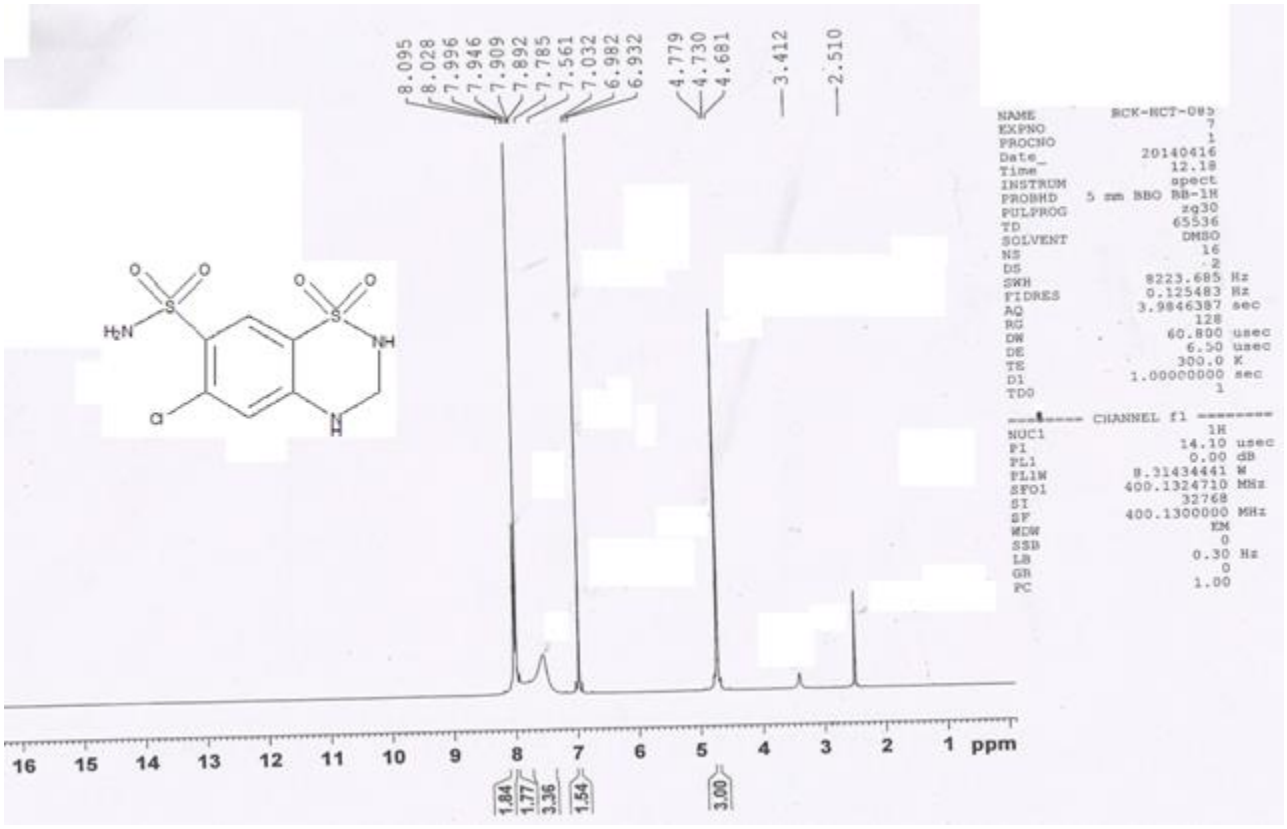
Detector A Ch1 250nm

Peak#	Name	Ret. Time	Area	Area %	RRT
1		1.51	1083	0.00	0.07
2		5.31	2803	0.01	0.25
3		8.81	4718	0.02	0.42
4		16.70	1091	0.00	0.79
5		20.33	376134	1.30	0.96
6	Stage-1	21.20	28503538	98.63	1.00
7		24.07	4321	0.01	1.14
8		32.64	2552	0.01	1.55
9		47.31	1925	0.01	2.24
Total			28898165	100.00	

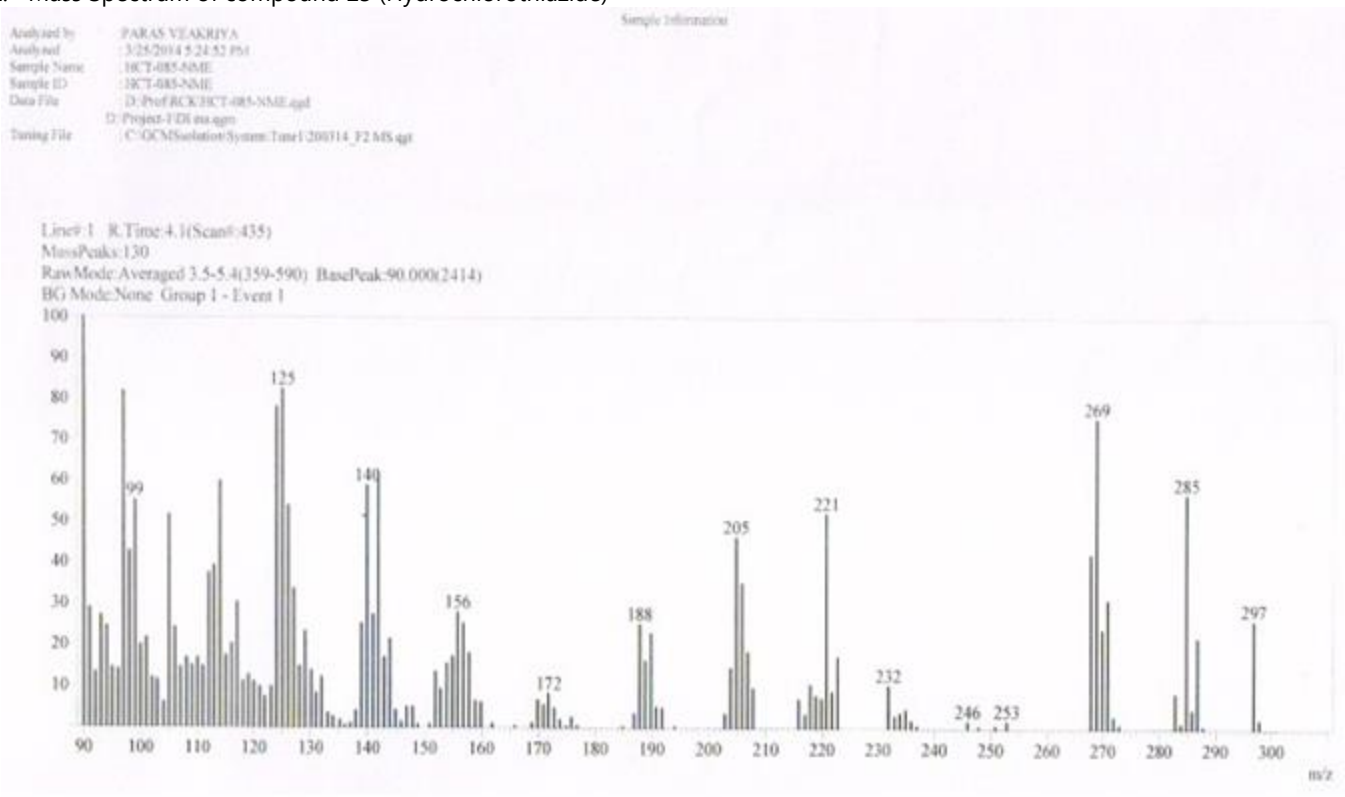
Figure 8

Spectra of compound 23 (Hydrochlorothiazide)

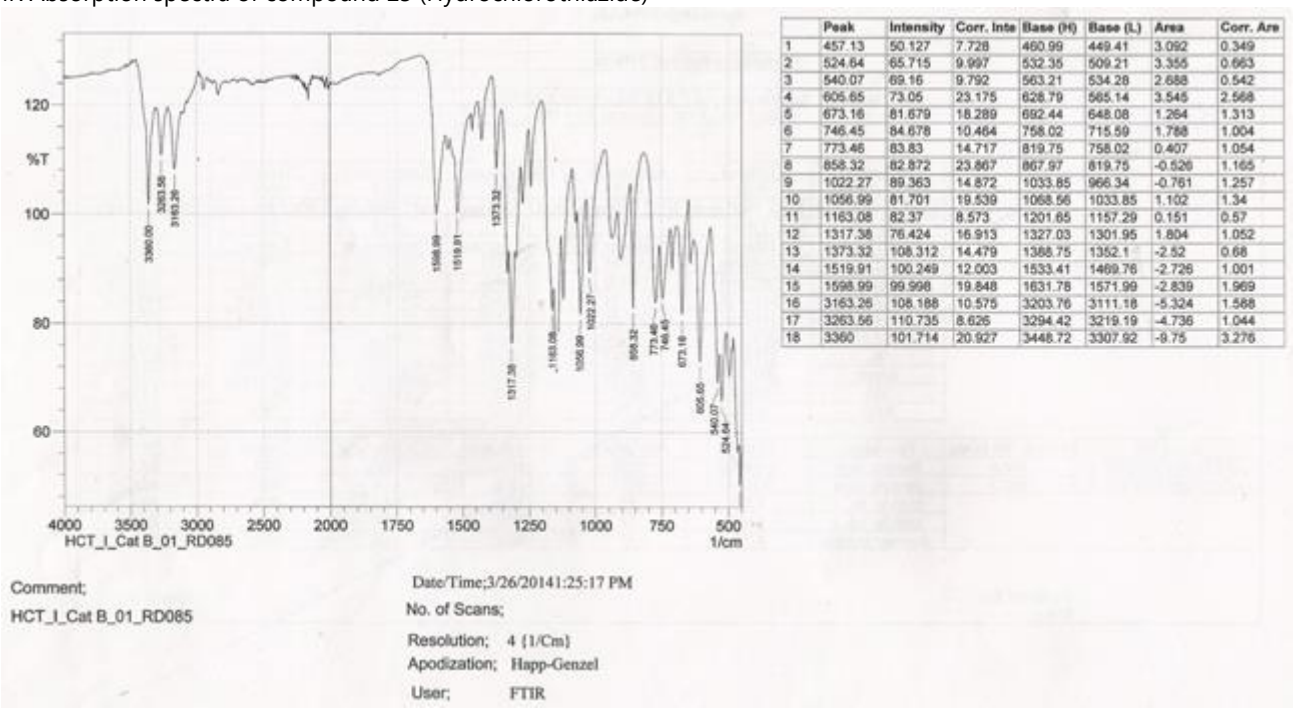
8.1. [1]HNMR of compound 23 (Hydrochlorothiazide) 400 MHz (DMSO)



8.2. Mass Spectrum of compound 23 (Hydrochlorothiazide)



8.3. IR Absorption spectra of compound 23 (Hydrochlorothiazide)

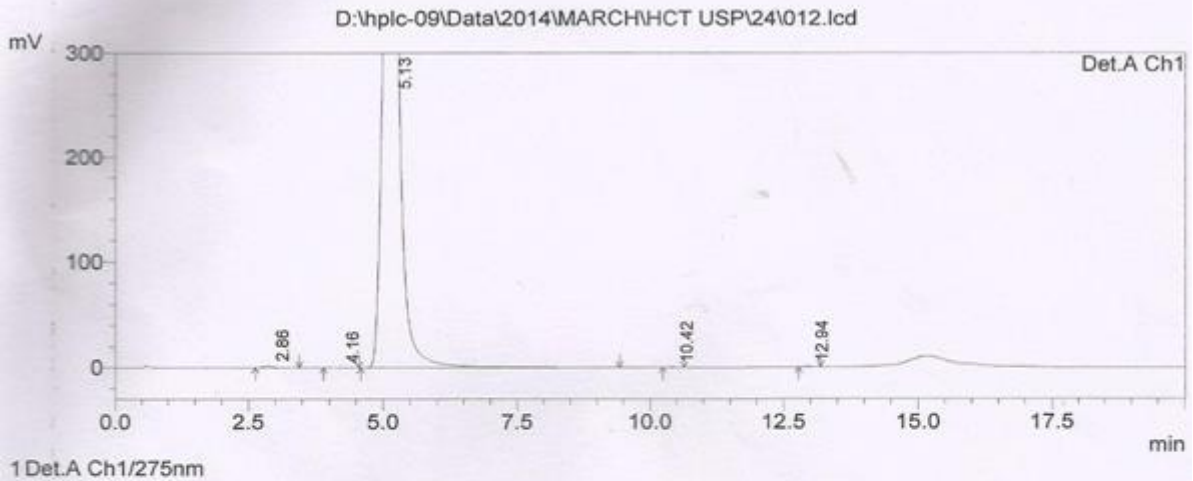


	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	457.13	50.127	7.728	460.99	449.41	3.092	0.349
2	524.64	65.715	9.997	532.35	509.21	3.355	0.663
3	540.07	69.16	9.792	563.21	534.28	2.688	0.542
4	605.65	73.05	23.175	628.79	565.14	3.545	2.568
5	673.16	81.679	18.289	692.44	648.08	1.264	1.313
6	746.45	84.678	10.464	758.02	715.59	1.788	1.004
7	773.46	83.83	14.717	819.75	758.02	0.407	1.054
8	858.32	82.872	23.867	867.97	819.75	-0.526	1.165
9	1022.27	89.363	14.872	1033.85	966.34	-0.761	1.257
10	1056.99	81.701	19.539	1068.56	1033.85	1.102	1.34
11	1163.08	82.37	8.573	1201.65	1157.29	0.151	0.57
12	1317.38	76.424	16.913	1327.03	1301.95	1.804	1.052
13	1373.32	108.312	14.479	1388.75	1352.1	-2.52	0.68
14	1519.91	100.249	12.003	1533.41	1469.76	-2.726	1.001
15	1598.99	99.998	19.848	1631.78	1571.99	-2.839	1.969
16	3163.26	108.188	10.575	3203.76	3111.18	-5.324	1.568
17	3263.56	110.735	8.626	3294.42	3219.19	-4.736	1.044
18	3360	101.714	20.927	3448.72	3307.92	-9.75	3.276

8.4. HPLC Purity of compound 23 (Hydrochlorothiazide)

Acquired by : Admin
Sample Name : HCT USP
Sample ID : HCT/I/CAT B/01/RD085_01
Injection Volume : 10 uL
Data Filename : D:\hplc-09\Data\2014\MARCH\HCT USP\24\012.lcd
Method Filename : D:\hplc-09\Method\Hydrochlorothiazide_USP.lcm
Date Acquired : 3/25/2014 12:56:34 AM
Data Processed : 3/25/2014 11:20:49 AM
Description : Column ID No.: ADL/COL/067

<Chromatogram>



1 Det.A Ch1/275nm

<Results>

Detector A Ch1 275nm

Peak#	Name	Ret. Time	Area	Area %	RRT
1	Impurity A	2.86	20319	0.17	0.56
2	chlorothiazide	4.16	2431	0.02	0.81
3	Hydrochlorothiazide	5.13	11976371	99.73	1.00
4	5-Chlorohydrochlorothiazide	10.42	2997	0.02	2.03
5	Dimer imp.	12.94	6629	0.06	2.52
Total			12008745	100.00	

5. CONCLUSION

We have provided a novel, cost-effective, industrially scalable and eco-friendly manufacturing processes of different antihypertensive intermediates that are substantially free from impurities and meet the regulatory norms in terms of quality within the same yield area. Also we have tried to reach the value of E – Factor towards zero i.e. 4.1 – 17.5, which is comparatively lesser than that for pharmaceuticals industries 25 - >100 so the novel methodology is greener than that for conventional procedure. Hydrotalcite is proven to be a green catalyst as there is reflection of sustainability from the above research work.

SUMMARY OF RESEARCH

1. An application of Hydrotalcite as green catalyst for proton abstraction which is responsible for enhancement of reaction is a novel effort in the direction of nature conservation.
2. N-alkylation of 1° and 2° amines by Hydrotalcite as catalyst is a novel approach for pharmaceuticals industries. Application of conventional bases i.e. metal hydroxides, metal carbonates, bicarbonates, several amine based organic bases can be eliminated on large scale industrial production by replacing them with catalytic amount of recyclable Hydrotalcite. Also yield and purity obtained is good by usage of it.
3. All the intermediates obtained are characterized by spectral techniques i.e. ^{1}H – NMR, FT – IR and Mass. Their purities have tested on HPLC by using validated analytical method.
4. Concept of E – Factor calculation and its comparison is novel approach in this research article. It is merely to have awareness towards the present trends of industries.

FUTURE ISSUES

I thought that my colleagues may face a problem regarding O-alkylation reaction by using hydrotalcite as base catalyst. As in comparison with Nitrogen, Oxygen possesses two loan pairs of electron, this may demands higher basicity which is not possible for present protocol of Hydrotalcite.

DISCLOSURE STATEMENT

There is no special financial support for this research work from the funding agency.

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